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RELATION OF DOSAGE SCHEDULE TO THERAPEUTIC EFFICIENCY OF STREPTOMYCIN IN THE TREATMENT OF K. PNEUMONIAE INFECTIONS IN MICE[1]

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Received for publication August 4, 1947

Keefer (1) states that in the treatment of infections in man with streptomycin it is necessary to give intramuscular injections every 3–4 hours. Paine, Murray and Finland (2) conclude that 1.0 g. of streptomycin every six hours is adequate for most infections. There is no experimental evidence to indicate that such frequent administration is essential for the optimal antibacterial efficiency of streptomycin. In several different infections in mice, it has been possible to obtain a high survival rate with a single intramuscular dose (3, 4, 5), or with two doses (6) of streptomycin. Single doses of 0.3 g. of streptomycin have been shown to cure gonorrheal urethritis (7).

Schedules of frequent administration of streptomycin in patients have been based possibly on analogy with the sulfonamides, with which drugs it is essential to maintain a blood concentration in order to obtain optimum effectiveness (8). It has recently been found (9) that aqueous penicillin G, in the treatment of hemolytic streptococcus infections in mice, is not demonstrably different in effectiveness whether given at twenty-four hour intervals or at one hour intervals. In other words, the antibacterial effect of penicillin G outlasts its presence in the mouse by many hours. Similar experiments were therefore undertaken to study the comparative effectiveness of streptomycin when administered at frequent and infrequent intervals to mice with a K. pneumoniae infection. The recent development of a chemical method (10) for streptomycin determination afforded an opportunity for a parallel study of the rate of disappearance of streptomycin from the blood of the same strain of mice.

[1] This investigation has been aided by a grant from the U. S. Public Health Service.

[2] Roche Fellow in Medicine and Experimental Therapeutics.

METHODS AND MATERIALS

1. *Mice.* The mice used in these experiments were albino mice of the Swiss strain, of uniform stock, from Tumblebrook Farm. The mice used in the infections weighed from 13–17 g., and those used in the plasma concentration studies weighed 18–21 g. For the infections

TABLE 1

Comparative therapeutic efficiency of streptomycin given intramuscularly in single and multiple doses to mice infected with K. pneumoniae

Mice: Tumblebrook Farm, albino, Swiss Strain, 13–17 g.
Organism: K. pneumoniae, Type B, Strain BE.
Infection: 0.5 ml. of 10^{-6} dilution of a 5 hour subculture, containing 7000 organisms.
Treatment: Streptomycin sulfate, intramuscularly, four hours after infection.

TOTAL AMOUNT OF STREPTOMYCIN BASE ADMINISTERED	PROPORTION OF SURVIVORS					
	Schedule					
	1	2	3†	4*	5†	6
	Untreated	Single Dose	3 Doses at 24 Hour Intervals	3 Doses at 8 Hour Intervals	3 Doses at 8 Hour Intervals	6 Doses at 4 Hour Intervals
mg./k.						
64	0/50	15/20	17/20		20/20	20/20
32		14/30	16/20	16/20	15/20	18/20
16		17/30	11/20	13/20	33/40	16/20
8		7/30	4/20	13/20	18/40	4/20
4		5/30	0/20	3/20	1/40	1/20
2		9/30	0/20	5/20	0/20	0/20
1		0/30			0/20	
½		0/30			0/20	
SD50 mg./k.		22.0	15.4	8.3	9.5	11.0
Standard Error ± mg./k.		4.8	2.1	2.4	0.8	1.3

* ½ the total dose given in first dose, remainder in ¼–¼ fractions.
† Three equal doses.

three separate experiments were run, and, since the results were highly reproducible, they have been pooled (Table 1). The first experiment was a small one, designed to determine the dosage range for subsequent study. Groups of ten mice were infected and treated as an experimental unit, each unit receiving a single dose of streptomycin. In the second and third experiments twenty mice were used as a treatment unit for each variation in either the amount or timing of

streptomycin dosage. In the second experiment a single dose was compared to three doses at eight hour intervals, at eight different dosage levels. In the third experiment, schedules 3, 4, and 6 (Table 1) were compared to three doses at eight hour intervals. In each experiment the first and last groups of mice infected were held as untreated controls.

2. *Klebsiella Pneumoniae Infection.* The mice were infected with K. pneumoniae, Type B, Strain BE. Stock cultures were grown in trypticase-soy-phosphate rabbit blood broth, and were kept at 6°C. Virulence was maintained by frequent mouse passage. Virulence studies showed that 700 organisms (0.5 ml. of a 10^{-6} dilution) injected intraperitoneally killed all but an occasional mouse. Ten to a hundred organisms killed about half the mice. For the experimental work, mice were injected intraperitoneally with 0.5 ml. of a 10^{-6} dilution of a five hour blood broth culture. This inoculum averaged 7000 organisms and killed all untreated control mice. Deaths of 85 per cent of the controls occurred in 10–24 hours. The remainder died in 2–10 days. Cultures of heart bood from the two controls dying on the 7th and 10th days, respectively, yielded K. pneumoniae. Similar cultures of one-third of the treated mice dying after day 10 were made and also grew out K. pneumoniae.

3. *Streptomycin.* A single lot (Pfizer-P4718) of amorphous streptomycin sulfate was used for both the treatment and plasma concentration studies. Chemical assay by the method of Marshall, Blanchard and Buhle (10) showed that 77 per cent of this material was streptomycin base. Ninety-five per cent of the base was streptomycin A, as shown by counter-current distribution studies (11). Dosage was calculated in terms of streptomycin base per kilogram of mouse. Injections were made intramuscularly in 0.2 ml. volume, four hours after infection. Only those mice still alive 21 days after the end of treatment were counted as survivors.

At any given dosage level, the mice in the different dosage schedules received the same total dose of streptomycin base.

4. *Plasma Concentration of Streptomycin in Mice.* A large number of mice were injected intramuscularly with 50 mg./k. of streptomycin sulfate in saline solution containing 5 mg. of the base per ml. Groups of mice were bled at 15, 30, 60 and 120 minutes after injection, 0.25 ml.

of whole blood being obtained from each mouse by cardiac puncture. If less than 0.25 ml. was obtained, the sample was discarded and the next mouse bled. Blood from ten or more mice for each time interval was pooled in a centrifuge tube containing one drop of 30 per cent sodium oxalate per 3.0 ml. of whole blood. The tube was centrifuged

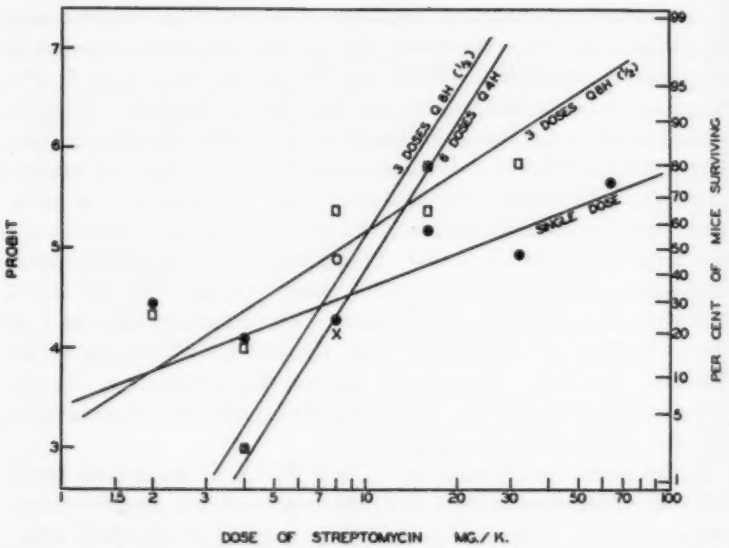

FIG. 1. Effect of intramuscular streptomycin upon survival rate of mice infected with K. pneumoniae (data taken from Table 1.)

●——● single doses.
○——○ 3 equal doses given at 8 hour intervals.
×——× 6 equal doses given at 4 hour intervals.
□——□ 3 doses at 8 hour intervals, given in $\frac{1}{2}$–$\frac{1}{4}$–$\frac{1}{4}$ fractions.

immediately, the plasma pipetted off, and the concentration of streptomycin determined by the method of Marshall, Blanchard and Buhle (10).

RESULTS

The results of the three experiments with K. pneumoniae infections are pooled in Table 1. The method of Litchfield and Fertig (12) has

been utilized for the calculation of the Median Survival Dose (SD50) and the standard error of the SD50.

1. *Effect of a Single Dose of Streptomycin.* When the K. pneumoniae-infected mice were given the entire amount of streptomycin in a single dose, erratic results are obtained (Table 1). Low doses

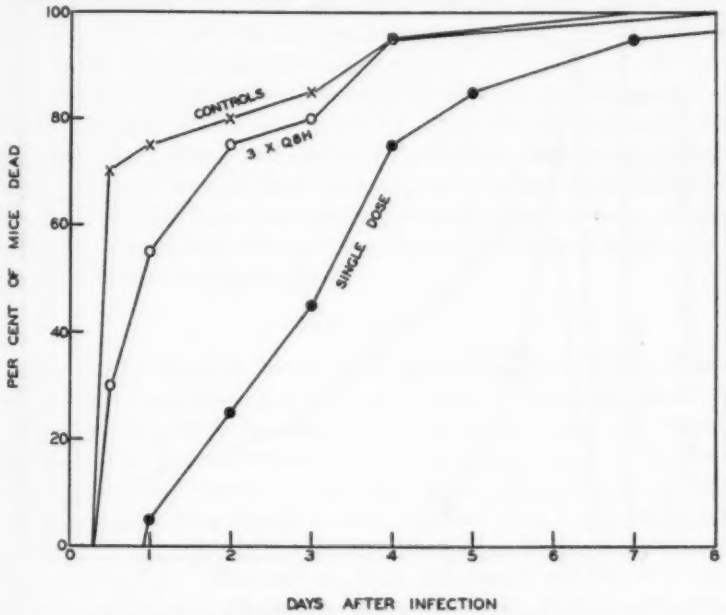

FIG. 2. Time of death of mice infected with K. pneumoniae, and receiving 1 mg./k. of streptomycin I. M. Each curve represents the cumulative deaths of 20 mice.

●——● single dose.
○——○ 3 equal doses given at 8 hour intervals.
×——× untreated mice.

saved significant numbers of mice, but even the largest doses tried failed to save more than 75 per cent of the mice. For this reason Median Survival Doses do not form an adequate basis for comparison of this dosage schedule with those which give 100 per cent survival, such as 5 and 6 of Table 1.

In Figure 2 is shown the effect of a single dose of 1 mg./k. of streptomycin upon the length of survival of the mice. This is compared to the effect of the same total dose split into three fractions, given at eight hour intervals. It can be seen that even though all the mice

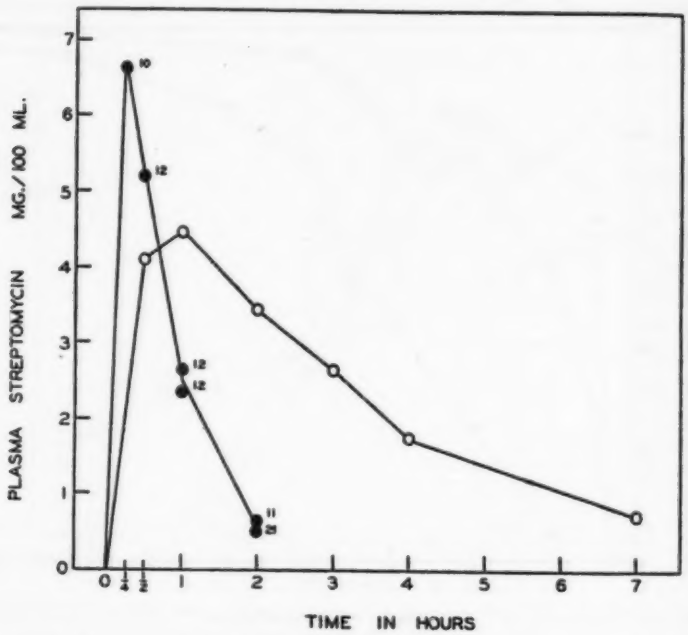

FIG. 3. Plasma concentrations of streptomycin in mice ●——● receiving 50 mg./k., and man ○——○ receiving 20 mg./k. in a single intramuscular dose. The numbers to the right of the solid circles represent the number of mice used for the determination.

ultimately die, longer protection was secured from the single dose than from the multiple doses.

2. *Effect of Multiple Doses of Streptomycin upon Therapeutic Efficiency.* When streptomycin is given in the treatment of K. pneumoniae-infected mice, there is no significant difference between a regimen of three doses at eight hour intervals and six doses at four

hour intervals (Table 1 and Figure 1). If the drug is given once every 24 hours for three doses, slightly larger amounts are required for the SD50. It is interesting to note in Figure 1 that dosage schedule 4 (three doses at eight hour intervals, with one-half the total amount given in the first dose) gives a dosage response curve intermediate in position between the single and other multiple dose curves. The "priming" dose given in the beginning apparently carries with it some of the characteristics of a single dose.

3. *Plasma Concentration of Streptomycin in Mice after Intramuscular Administration.* These are shown in Figure 3, together with the plasma concentrations obtained in man after a single intramuscular dose. Despite the fact that the mice, on a weight basis, received two and one-half times the quantity of drug given to man, plasma concentrations of above 0.5 mg. per cent are maintained in the mice for one-fourth as long as in man.

DISCUSSION

The dosage schedule (six doses at intervals of four hours), which most nearly approximates a constant plasma concentration in mice, is not significantly better than schedules of less frequency (three doses at eight hour intervals), and is only slightly superior to three doses at 24 hour intervals. Many other dosage schedules, particularly those involving more frequent administration, require testing before selection can be made of the maximally efficient therapeutic regimen for streptomycin. Nevertheless, from the data available, it is apparent that frequent dosage is not essential for the efficient utilization of streptomycin in K. pneumoniae infections in mice. In this respect, streptomycin resembles penicillins G and K (9) rather than the sulfonamides (8).

The comparative plasma concentration of streptomycin, after single intramuscular doses in mouse and man, indicates that the entire cycle of absorption of streptomycin from muscle, and disappearance from the plasma, is much more rapid in the mouse—two hours of equivalent plasma concentration in the mouse corresponding to about eight hours or more in man.

These facts and conclusions about the antibacterial effect of streptomycin in K. pneumoniae infections in mice are not necessarily

transferrable to the treatment of human infections. However, these experiments indicate that it is probably unnecessary to administer streptomycin to man in such a fashion as to maintain constant plasma concentrations. On that basis alone, because of less pain and more rest for the patient, schedules of less frequent administration are worthy of trial in human infections. When, in addition, one considers that a constant plasma concentration of streptomycin has been associated with the rapid emergence of resistant organisms, and with considerable human toxicity, further need for such trial becomes apparent. It is important to point out that trials of infrequent administration of streptomycin should be undertaken in carefully selected cases and under close observation. Specific suggestions for dosage regimens in streptomycin-susceptible infections in man cannot be extensive as each case presents its own problem. However, it seems justifiable to proceed with a dose of 1.0–2.0 g. intramuscularly every 12 or 24 hours, in acute infections, until the temperature is normal. In fulminating infections, it is probable that small fractions of streptomycin given at frequent intervals may fail to control the large bacterial population. Hence it is suggested that a "priming" dose of 2.0 g. be given such patients as soon as possible. Larger single doses should not be given unless it can be shown that toxicity is a function of long continued constant plasma concentration, rather than of peak concentrations.

SUMMARY

1. In the treatment of mice with K. pneumoniae peritonitis with intramuscular streptomycin, there is no significant difference in results between schedules of administration at four hour intervals or at eight hour intervals.

2. When single doses of streptomycin were used, large increments in dosage gave only small changes in survival percentages of the mice.

3. Mouse plasma streptomycin concentrations remained above 0.5 mg. per cent for two hours after a single intramuscular dose of 50 mg./k. In man, after a single dose of 20 mg./k. plasma concentration remained above 0.5 mg. per cent for seven hours.

4. The implications of these experimental findings in the treatment of streptomycin-susceptible infections in man have been discussed.

The author wishes to thank Dr. E. K. Marshall, Jr. for helpful advice; Dr. Harold J. White, American Cyanamid Co., for the K. pneumoniae; Dr. Oskar Wintersteiner, of the Squibb Institute for Medical Research, for the counter current distribution studies; Dr. R. A. Patelski, of Chas. Pfizer and Co., for the streptomycin sulfate; and Mrs. Evelyn Epperson for technical assistance.

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STUDIES ON SCHISTOSOMIASIS JAPONICA IN THE PHILIPPINE ISLANDS

3. A Clinical Study of 72 Cases Treated with Tartar Emetic

DOUGLAS CARROLL* and ARNE V. HUNNINEN†

Received for publication Aug. 4, 1947

The epidemic of Schistosomiasis japonica which occurred on Leyte, Philippine Islands, started in November 1944, reached its peak in January and died out in May of 1945. Billings, Winkenwerder and Hunninen (1) reported on the signs and symptoms of the acute stage. A second report by Winkenwerder et al (2) is an analysis of the effect of treatment with 40 cc. of Fuadin. The present report concerns 72 patients treated with tartar emetic, 32 of whom were followed into the seventh month of their illness. The use of tartar emetic in such a large group of acute cases of schistosomiasis has not been previously reported.

MATERIAL AND METHODS

1. *Onset, diagnosis and incubation period:* All the patients in the present series had the onset of the acute symptoms in late January or early February of 1945. The diagnosis was made in all cases by the finding of mature ova of Schistosoma japonicum in the stool specimen. All patients were American soldiers not previously exposed to this disease. The average incubation period for 68 cases was 50.2 days.

2. *Severity of symptoms:* The incidence of acute symptoms and the physical findings parallel those reported by Billings, Winkenwerder and Hunninen. Five cases were severe, 31 moderately severe, 32 mild, and 4 were asymptomatic. The last group was discovered on routine stool examination.

3. *Treatment:* 1.89 gm. of tartar emetic was used in the treatment of this series. A solution of 0.4 gm. tartar emetic per 100 cc. of 5 per cent dextrose-physiological saline was made up under sterile conditions. The solution was never heated and was used within three hours of mixing. It was given intravenously every other day for eight-

* Capt., M.C., AUS.
† Capt., Sn.C., AUS.

een doses. The first dose was 0.020 gm. of tartar emetic or 5 cc. of the solution. The second dose was 0.040 gm., the third dose 0.060 gm., the fourth 0.090 gm., and thereafter all doses were 0.120 gm. or 30 cc. of the solution. In the first four doses the solution was diluted with 5 per cent dextrose-physiological saline to make 30 cc. of liquid injected. It was given over a period of about ten minutes into the antecubital vein in a 30 cc. syringe.

3a. *Treatment reactions:* Chart number one shows that there were a great many minor reactions to treatment and four severe reactions necessitating discontinuance of the tartar emetic. The cough, nausea and vomiting were acute symptoms starting while the tartar emetic was being injected. The stiffness of the joints came on later and became worse gradually as more of the drug was given. The cough was prevented or decreased in many cases by giving 0.0006 gm. of atropine orally one half hour before injection.

3b. *Retreatment with 40 cc. of Fuadin:* Of the 72 patients who completed the course of tartar emetic, 32 were retreated with 40 cc. of Fuadin one month after the tartar emetic course was finished. These patients were retreated because degenerated eggs were found in their stools in the third and fourth week after tartar emetic treatment. None of these patients had immature eggs. Because the significance of degenerated eggs was not known, retreatment was thought to be indicated. The Fuadin was given in eight consecutive daily doses of 5 cc. by the intramuscular route.

RESULTS

All patients were discharged to duty after hospitalizations ranging from one to four months. Thirty-two were available for study throughout the first seven months of their illness. Of these 14 had been retreated with 40 cc. of Fuadin. Subjectively few of the discharged patients felt perfectly well, although all carried on light duty. Complaints such as headache, nervousness, lassitude, and weakness were common. Many of these symptoms were thought to be on a functional basis, arising in a situation of uncertainty about the future, associated with changes in disposition policy and long hospitalizations (3).

1. *Clinical observations during the first seven months:* There was no

striking improvement with the institution of tartar emetic therapy. Of 31 patients weighed in the seventh month of their illness, 35 per cent had lost weight since the onset of the illness.

CHART 1

Reactions to tartar emetic treatment (in 72 patients)

DOSE	COUGH	NAUSEA	VOMITING	STIFFNESS	MISCELLANEOUS
1	1	3	0	0	
2	1	3	1	0	
3	3	4	1	0	
4	11	7	2	1	
5	20	3	0	2	Purpura*
6	16	2	0	2	
7	13	5	2	2	Substernal pain*
8	15	7	3	4	
9	14	3	1	5	Vascular collapse*
10	16	4	2	5	
11	15	2	1	6	
12	17	6	4	7	
13	15	10	6	11	
14	16	4	0	19	
15	15	10	3	20	
16	16	9	3	28	
17	17	9	4	39	Cough, diarrhea, vomiting*
18	13	11	5	38	

* Severe reactions necessitating discontinuance of tartar emetic.

CHART 2

Change in physical findings with time

PHYSICAL FINDING	MONTH			
	1	2	3	7
General glandular enlargement	33*	35	6	—
Cervical glandular enlargement	31	19	13	—
Palpable liver	29	24	11	12
Palpable spleen	28	7	3	3
Total cases	72	70	62	31

* All figures except those in the lowest horizontal line are in percentages.

General glandular enlargement was not appreciable after the third month of the illness (chart number two). Cervical glandular enlarge-

ment persisted slightly longer than general glandular enlargement. Chart number two shows the hepatic and splenic indices in the first, second, third and seventh months.

2. *Laboratory observations during the first seven months:* Chart number three shows that the leucocyte count approached normal as time passed. Retreatment with Fuadin did not significantly influence the average leucocyte count as compared with the unretreated group. The absolute eosinophile count also approached normal as time passed, as is shown in chart number four.

CHART 3

Fall in leucocytes with time

LEUCOCYTES	ONSET	MONTHS				
		1	2	3	4	7
thousands						
35+	3.2*					
30+†	3.2					
25+	3.2					
20+	12.9	3.2				
15+	24.3	12.7	1.5	5.5		
10+	37.1	42.8	19.7	10.9	19.7	12.9
5+	16.1	38.7	74.2	80.0	77.0	74.2
2+	0.0	1.6	4.6	3.6	3.3	12.9
Total cases.....	62	63	66	55	61	31

All figures are in percentages except the column of the left and the lowest line.

* Two leucocyte counts were above 35.0 thousand. One was 54.9 and the other 45.9 thousand.

† 30+ represents all leucocyte levels between 30.0 thousand and the figure directly above it, in this case 35.0 thousand.

Twenty-six patients had hematocrits performed and 29 had sedimentation rates done in the seventh month, and all were normal.

Stool examinations were done twice weekly following treatment until the seventh month of the illness (fifth month post tartar emetic treatment). As time went on, patients were lost through rotation and troop movements. In the seventh month, all patients who could be reached were hospitalized and examined completely. There were 32 patients followed into the seventh month. Two patients showed mature eggs of Schistosoma japonicum in the sixteenth week post

CHART 4

Fall in eosinophiles with time

ABSOLUTE EOS. LEVEL	ONSET	MONTH				
		1	2	3	4	7
thousands						
16+	6.6*					
15+†	3.2	1.5				
14+	0.0	0.0				
13+	1.6	0.0				
12+	8.2	1.5				
11+	4.4	0.0				
10+	6.6	3.0				
9+	4.9	1.5				
8+	4.9	7.9				
7+	6.6	3.0				
6+	4.9	4.7	3.0		1.7	
5+	19.6	6.3	3.0		0.0	
4+	6.6	9.5	7.5		0.0	
3+	6.6	27.0	0.0		1.7	
2+	3.3	12.6	7.5		1.7	3.2
1+	3.3	9.5	37.9	27.3	25.4	9.7
0.2+	4.9	7.9	30.3	41.8	44.1	38.7
0.0+ (normal)	3.3	3.0	10.6	30.9	25.4	48.4
Total cases.....	61	63	66	55	59	31

All figures are in percentages except the left column and the lowest line.

* Four absolute eosinophile counts were above 16.0 thousand. They were 45.9, 25.8, 21.8 and 18.0 thousand.

† 15+ represents all eosinophile levels between 15.0 thousand and the figure directly above it, in this case 16.0 thousand.

CHART 5

Incidence of positive stools for mature ova of schistosoma japonicum in the months following treatment with tartar emetic (includes cases treated with Fuadin)

	MONTHS POST TARTAR EMETIC TREATMENT					
	0	1	2	3	4	5
Number of cases showing mature ova of Schistosoma japonicum.....	72	0	0	0	2	2
Total cases.....	72	71	71	42	25	32

tartar emetic treatment and 2 others in the seventeenth week (chart nunber five). Of these 4, 3 had been retreated with 40 cc. of Fuadin. Only one of this group had changes on sigmoidoscopy.

3. *Sigmoidoscopy:* All 32 patients available in the seventh month of the illness (fifth month post tartar emetic treatment) were sigmoidoscoped. Of these, 8 showed nodules in the rectum or sigmoid of the type described by Johnson and Berry (4). Only one of these had a positive stool. Four had been retreated with 40 cc. of Fuadin. All patients with positive stools or nodules in the lower intestine were considered to have recurrences and were retreated with 60 cc. of Fuadin in 5 cc. daily doses intramuscularly without any reactions.

DISCUSSION

An analysis of the cases having recurrences, as determined by either a stool or sigmoidoscopic examination in the seventh month, was made with regard to severity at onset, leucocytosis and eosinophilia at onset and in the seventh month, as well as the number retreated with 40 cc. of Fuadin. There was no significant difference between the cases which recurred and those which did not in regard to the original leucocytosis and eosinophilia or for these values at the end of seven months. Retreatment with Fuadin had no effect on preventing recurrences. None of the asymptomatic cases recurred. Otherwise, the clinical severity of the disease at onset did not influence the recurrence rate.

It was our impression that the patients treated with tartar emetic had fewer recurrences than a comparable group (1, 2) treated with Fuadin alone in the same hospital.

SUMMARY

Seventy-two cases of acute Schistosomiasis japonica were treated with intravenous tartar emetic. Thirty-two cases showing degenerated eggs in the third and fourth week after the tartar emetic course was finished were retreated with 40 cc. of Fuadin. Of the whole group, 32 were followed into the seventh month of their illness (five months post tartar emetic treatment). Findings on physical examination, on the leucocyte and eosinophile counts, as well as on stool examination, are present in chart form for the first seven months of the illness.

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THE CLINICAL USE OF PENICILLIN IN OIL AND BEESWAX IN PEDIATRIC PRACTICE

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Most of the reports concerned with the clinical application of penicillin suspended in peanut oil and beeswax (hereafter to be designated as P.O.B.) have dealt with its use in adults, particularly as a therapeutic weapon in gonorrhea and syphilis. Various authors (1, 2, 3) have clearly shown that uncomplicated gonococcal urethritis can be treated successfully with a single injection of P.O.B. Romansky (4), in a comprehensive review of 600 cases of various pyogenic infections treated with calcium penicillin in oil and beeswax, concluded that the results obtained were as satisfactory as with those treated by multiple injections of aqueous penicillin. There were forty-two cases of pneumococcal pneumonia included in his series, ten of which were in children under sixteen years of age. The results were apparently good inasmuch as only four of the patients required more than four days of treatment to clear the infection.

If one is able to maintain a satisfactory therapeutic level of penicillin for twenty to twenty-four hours by this method of injection, its clinical application in Pediatrics at once becomes apparent. As is well known, in children the associated symptoms of vomiting and failure to take fluids with almost all pyogenic infections sometimes make sulfonamide administration difficult. For this reason, many children have to be hospitalized for the sole purpose of aqueous penicillin therapy. The economic and therapeutic value of being able to treat these children at home with single daily injections of P.O.B. is quite obvious. With these objectives in mind a clinical study of P.O.B. was carried out in an active pediatric dispensary.

METHOD OF STUDY

Between January 1, 1947, and April 15, 1947, one hundred consecutive cases of pneumonia were treated with P.O.B. These patients

were completely studied with cultures, X-rays, and penicillin blood assays. In addition to the pneumonia group several other disease entities were treated with P.O.B., but without bacteriological studies. In these, only clinical impressions are available and will be discussed briefly later.

For the most part, these children were treated as ambulatory patients, necessitating daily visits to the clinic for their P.O.B. injections and follow-up care. Hospitalization was carried out only in the cases of severe pneumonia in which the treatment had to be supplemented with appropriate measures to correct associated dehydration, heart failure, cyanosis or severe anemia. Seven such children were hospitalized and received P.O.B. In addition, three of the patients on whom treatment with P.O.B. was unsuccessful were also hospitalized for sulfadiazine therapy.

The diagnosis of pneumonia was based on definite positive physical findings or X-ray evidence of pneumonic infiltration, or both. Once the diagnosis of pneumonia was made, nasopharyngeal and throat cultures were taken.

Throughout the study crystalline sodium penicillin suspended in peanut oil with 4.8 per cent (w/v) bleached beeswax was used. This was supplied in ten cubic centimeter vials containing 300,000 units per cubic centimenter[1]. All patients received 5,000 units per pound at each injection.

The technique of withdrawing the P.O.B. from the vial and injecting the contents intramuscularly with the use of 20-gauge needles and dry sterilized Luer-Lok syringe was that advocated by Romansky (4). However, for the most part, the P.O.B. was not allowed to cool to room temperature prior to injection. We found that when giving relatively small doses to infants, the use of tuberculin syringes facilitated calibrating the amount given, with reasonable accuracy. All the injections were given intramuscularly, deep into the gluteal group of muscles. Subcutaneous administration was not used.

Treatment was carried out with the use of single daily injections until such time that the patient's clinical response was adequate and the temperature had returned to normal. Two further daily injections were then given and the child's course followed for one more week.

[1] The P.O.B. was kindly furnished by E. R. Squibb and Sons.

On the child's second visit to the dispensary, which was usually eighteen to twenty-four hours after the initial injection of P.O.B., blood was drawn for penicillin assay. Except for patients who were hospitalized, only a single penicillin assay was made on each child. With those children who were admitted to the hospital, two or three assays were obtained within a twenty-four hour period.

Most of the patients had chest X-rays taken on the first day of treatment. Thereafter, they were followed fluoroscopically and the X-rays were repeated in seven to ten days time on only those patients in which the response was either slow or a failure.

The final part of the study was carried out in an attempt to demonstrate any sensitivity that these patients may have developed to any of the constitutent parts of the penicillin in oil and beeswax mixture. These results will be discussed in detail in a subsequent section.

THE PNEUMONIA SERIES

There were sixty-four males and thirty-six females in this group of 100 patients. Eighty-six were negroes and fourteen were white. Their ages ranged between two months and eleven years with fifty-seven of the children under two years of age, thirty-two of these being under twelve months. The remaining forty-three were in the age group between two and eleven years. Thus, a good proportion of the cases in our series were in the age group under two years, a group in which the mortality rate prior to the chemotherapeutic era ranged between twenty and thirty-five per cent.

Type of Pneumonia: For the purposes of clinical classification we have designated all cases with localized homogeneous consolidations as lobar pneumonia, while those with scattered patchy diffuse infiltrations were classified as bronchopneumonia. Under this rather broad classification the following types of pneumonia were observed:

	BRONCHOPNEUMONIA	LOBAR PNEUMONIA
Under two years of age	24	33
Over two years of age	11	32
Total	35	65

Etiological Agents: Hodes et al (5) have pointed out that in cases of pneumonia the pneumococci obtained from the nasopharynx were almost always of the same type as that recovered from the blood stream, empyema fluid, middle ear or cerebrospinal fluid of the same patient. They concluded that the pneumococci isolated from the nasopharynx were etiologically more significant than those recovered from the throat.

Results of our cultures for pathogenic organisms, the great majority of which were recovered from the nasopharynx, are tabulated below.

Pneumococcus type 4	4.	Pneumococci present in 78% of the cases
Pneumococcus type 6	14.	
Pneumococcus type 14	19.	
Pneumococcus type 19	9.	
Pneumococcus type 23	5.	
All other types	27.	
beta hemolytic Streptococcus alone	5	
beta hemolytic Streptococcus with pneumococcus	14	
hemolytic Staphylococcus aureus	5	
H. influenzae B with pneumococcus	2	
H. influenzae (negative quelling types A and B) with pneumococcus	7	
Negative cultures	6.	12%
Unsatisfactory cultures	6.	

Clinical Results: The clinical results of treatment were classified as either good, poor, or as failures.

A good result entailed an adequate response, with complete subsidence of the pneumonic infiltration along with clinical improvement in a reasonable length of time, with the only chemotherapeutic agent being P.O.B. Further subdivision of the good results into rapid and slow responses seemed of value. The response was considered rapid when the patient attained a normal temperature within forty-eight hours and was relatively asymptomatic within four days. All other patients who attained an ultimate good result, clearly influenced by the chemotherapy, but in a longer time, were considered to have a slow response.

Classified as poor results are those patients in whom there appeared to be an inadequate response to P.O.B. in the length of time that was required to bring the infection under control, or in which some complication, such as otitis media, developed while the P.O.B. was being given. Cases were classified as failures when sulfadiazine or aqueous

penicillin had to be given after the P.O.B. had failed to bring the pneumonia under control, or in which there was an exacerbation of the pneumonia.

As is indicated in Table I, 92% of the children had a good result with eighty-one responding in a rapid fashion and eleven slowly. There were four poor results and four patients that were classed as failures. There were no deaths in the entire group. In 96 cases, excluding the four failures, the temperature dropped to normal and remained there within an average of twenty-seven hours, with a range between twelve and one hundred and twenty hours.

This group of 100 patients received a total of 447 injections of P.O.B., averaging 4.5 injections per patient with a range of from two to nine injections.

TABLE I

RESULTS IN PNEUMONIA	GROUP
Good	92
Rapid	81
Slow	11
Poor	4
Failure	4
Total	100

Poor Responses to Treatment: Of the four patients for whom the results of treatment were considered to have been poor, all had rapid clearing of the original pneumonia. Nevertheless, these were considered to have shown a poor response because they developed otitis media under treatment. In two of these cases the organism was the same as that considered responsible for the pneumonia. In the third the otitis was due to *H. influenzae B.* All of these complications cleared slowly on sulfadiazine therapy. The fourth child had chronically infected adenoids with recurrent upper respiratory tract infections.

Failures: In four of the cases the treatment was considered as having failed for the following reasons. The first patient maintained fever and signs of consolidation after six days of treatment, but recovered rapidly under sulfadiazine therapy. His nasopharyngeal

cultures yielded type 15 pneumococci, H. influenzae and Staphylococcus aureus.

The second patient had pneumonia with severe dyspnea and cardiac failure. Although his temperature reached normal within twenty-four hours, signs of consolidation persisted at the left base throughout seven days of P.O.B. therapy. Cultures yielded type 14 pneumococcus and beta hemolytic Streptococcus. Nine days after therapy was discontinued, he developed fever and X-ray evidence of interlobar fluid. Following no response to aqueous penicillin he recovered under sulfadiazine therapy.

The third case was complicated by a nutritional anemia and chronic upper respiratory tract infection. Type 6 pneumococci and beta hemolytic Streptococci were recovered from nasopharyngeal culture. Because of only gradual improvement during six days of P.O.B. therapy, he was hospitalized and improved rapidly following blood transfusions and aqueous penicillin therapy.

The fourth patient was a mentally retarded two and a half year old child with pneumonia (pneumococcus type 14). His temperature fell to normal within thirty-six hours and he was symptom-free in three days except for continued nasal discharge. He was treated for four days but, three days after discontinuance of P.O.B., developed fever, increased nasal discharge and rales throughout the lungs. He had a good response to a second course of three daily injections of P.O.B.

In each of the above cases there was some complicating factor on which the apparent failure of treatment might well be explained. It is deemed wisest, however, to consider that the treatment failed to accomplish the desired result in these patients.

Complications: Non-suppurative catarrhal otitis media occurred as a complication in seven of the 100 cases of pneumonia. Six of these were present at the time of the first visit and the other appeared on the fifth day of treatment.

Suppurative otitis media was seen in seven of the patients. Four of these were present on admission, while the remaining three developed on the third, fourth and fourteenth days respectively. In general, it was found that when otitis media complicated the pneumonia, the treatment with P.O.B. had to be continued for two to three days longer than when this complication was absent. As was shown in three of the poor results, sulfadiazine had to be added to the therapy

in order to clear up the otitis media, although the pneumonia responded well to P.O.B.

Atelectasis of a single lobe of the lung occurred definitely in two patients and was questionably present in two others. Neither of the two definite atelectases, one in the right upper lobe and the other in the right middle lobe, required bronchoscopy. Both cleared spontaneously in five to eight days time. The two questionable atelectases, both of the right middle lobe, also cleared spontaneously.

TABLE II

Infections Treated with P.O.B.

DISEASE	RESULTS		
	Good	Poor	Failure
1. Suppurative otitis media	17	0	1
2. Suppurative otitis media Sulfadiazine resistant	9	0	0
3. Severe Pharyngitis	10	1	0
4. Severe Pharyngitis and otitis media	7	2	0
5. Ulcerative Stomatitis	14	2	0
6. Furunculosis	2	1	0
7. Cellulitis	4	0	0
8. Suppurative Adenitis	4	0	0
9. Peritonsillitis	2	0	0
10. Conjunctivitis—Non-specific	2	0	0
11. Gonorrheal Vaginitis Sulfadiazine Resistant	2	0	0
Total	73	6	1

The fairly definite interlobar empyema that came on while the patient was being treated with P.O.B. has already been discussed as one of the failures. There were no cases of meningitis complicating the pneumonias.

OTHER INFECTIONS TREATED

Several other types of infections were also treated with P.O.B., but inasmuch as the bacteriologic workup was incomplete, only clinical impressions are available. There was a total of eighty such infections treated, the results of which are tabulated in Table II.

The results, in general, were quite satisfactory, particularly in regard to the twenty-sven cases of suppurative otitis media, nine of which had failed to respond to sulfadiazine therapy. With only one exception the aural discharge stopped within two to three days after the institution of P.O.B. therapy and the tympanic membranes healed rapidly. Four to five days of P.O.B. injections were sufficient to bring about these results.

P.O.B. significantly reduced the duration of symptoms in ulcerative stomatitis. Within twenty-four to forty-eight hours after the first injection these children showed marked improvement. Three daily injections were usually all that was necessary.

PENICILLIN ASSAYS

The serum assay method used was that originally described by Rammelkamp (6), with modifications according to Eagle (7, 8).

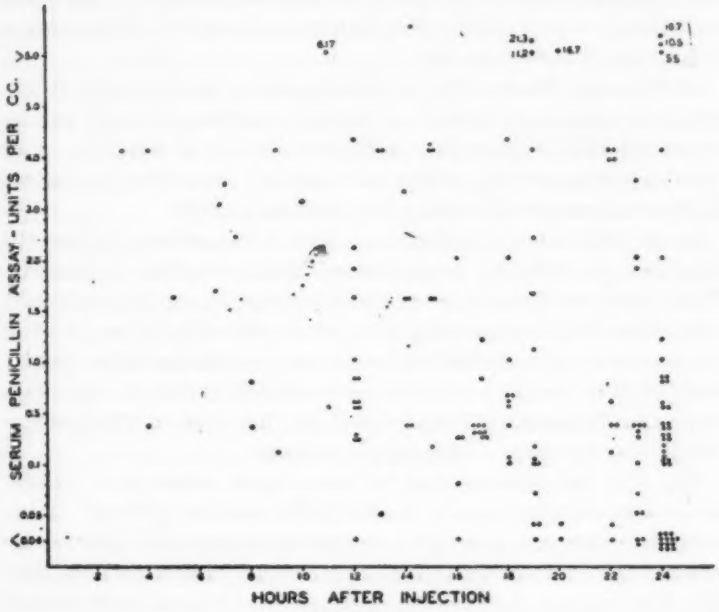
Graph I illustrates the composite picture of the 153 penicillin assays that were determined. One can see the tremendous variation in the levels that were present at any given hour. So great was the variability of these levels that we were unable to plot a mean curve which would be of any value. Of the seventy-one assays obtained in the period twenty-two to twenty-four hours after the injection of P.O.B., 18% showed no detectable titre (less than 0.03 units per cc.).

There are several possible factors that may be responsible for the great variability in absorption rate of penicillin when this agent is suspended in peanut oil and beeswax. First of all two different lots of P.O.B. were used throughout the study. In the latter half, the levels were much more consistent than during the time the first lot was used. The reasons for this discrepancy are not clear.

Secondly, Romansky (9) has shown that the rate of penicillin absorption is greatly dependent on the degree of muscular activity. If the P.O.B. is given in the late afternoon he has found that, with the decrease in muscular activity during the sleeping hours, there is a slower absorption of the penicillin during the first twelve hours. This then leaves a greater quantity of penicillin to be absorbed during the second twelve hour period, and consequently higher levels are obtained in the last four to six hours. Some of the variability in our patients' levels might well be accounted for along this line of reasoning,

for the injections were given at all hours during the day, the majority of them in the morning.

The factor of muscular activity and its consequent effect on the rate of absorption probably plays a more important role in children than in adults. It is difficult to keep a moderately ill child at low activity



GRAPH I

even in bed, although with seriously ill children activity is usually at a minimum. Therefore, it is reasonable to assume that there would be great variation in the absorption curves.

We must therefore draw the conclusion that it is impossible to be certain how long any given patient will have a titratable penicillin level following an injection of P.O.B.

REACTIONS TO P.O.B.

Romansky (4) in summarizing the use of P.O.B. on nearly 4,000 cases receiving 60,000 injections found only two instances of sterile

foreign body abscesses. Both of these were in patients who received the material subcutaneously. Allergic manifestations, characterized by reactions varying from slight urticaria to generalized angioneurotic edema occurred in about five per cent of his cases. It is Romansky's (9) opinion that these reactions with P.O.B. occurred only slightly more frequently than with the use of aqueous penicillin. There was no evidence of any paraffinomas developing in any of the patients in this large series of 4,000 cases.

Nichols and Haunz (10), in treating forty patients with P.O.B. given subcutaneously, found no allergic reactions and only two instances of mild inflammatory reaction at the site of injection. Such reactions are apparently much more commonly seen when the material is given subcutaneously rather than intramuscularly.

In our total series of patients, numbering 180 and representing 696 injections, we observed no generalized allergic reactions whatsoever. There were two instances of a mild inflammatory reaction with some induration of the surrounding tissue at the site of injection. One of these occurred when the material was given subcutaneously by mistake. Both of these reactions subsided spontaneously in two to three days time. As Romansky (4) has pointed out, this type of inflammatory change may represent a local allergic response.

Gay (11) has demonstrated the nonantigenic character of peanut oil-beeswax mixtures even in known pollen sensitive patients. However, with the slow prolonged absorption of penicillin afforded by suspending it in this peanut oil-beeswax medium, there is the possibility that these patients may develop sensitivity to the various components of the mixture, with subsequent allergic reactions.

With this possibility in mind, thirty-five of the children were tested for sensitivity two to four months after they had been treated with P.O.B. Each child received an intracutaneous injection of about 100 units of aqueous penicillin G and a similar injection of the peanut oil-beeswax vehicle. At the same time he was given an intramuscular injection of the same dose of P.O.B. previously used for daily treatment of his infection. These children were then detained in the clinic for one hour, during which time the skin tests were read and they were observed for any systemic reaction. At the end of one hour their temperatures were retaken and they were then sent home.

On return to the clinic the following day their temperatures were again recorded and they were examined for any sensitivity reaction. The visiting nurse services went into the homes twice during the three days of observation so that any of the allergic reactions would not be missed.

In this group of thirty-five children there was only one questionable allergic reaction. This was in a child of two years of age, who had a history of periodic attacks of urticaria. He had been treated for otitis media with P.O.B. two months prior to being tested. No allergic reactions were noted at that time. At the time that the skin tests were applied he had a few erythematous plaques scattered over the chest and abdomen. The skin tests were negative and he had no febrile response. Eight hours after being tested he was reported to have broken out with a wide spread urticarial eruption which lasted only about six hours. By the time he was seen the following morning the urticaria had completely disappeared. In view of the preceding allergic history, plus the fact that the skin tests were negative and the transitory character of the urticaria, we doubt that this represents a true allergic response to P.O.B.

The remaining thirty-four children elicited no allergic response, and all the intracutaneous tests were negative.

SUMMARY

1. One hundred and eghty children with various acute infections were treated, as out-patients, with penicillin suspended in a mixture of peanut oil and beeswax.

2. There were 100 consecutive cases of pneumonia, thirty-two of which occurred in infants under twelve months of age. The results achieved were quite satisfactory, with ninety-two good responses, four poor responses, and four failures.

3. Twenty-nine cases of suppurative otitis media, nine of which proved to be sulfadiazine resistant, were also treated. There was only one failure in this group.

4. The penicillin blood levels obtained by this method of injection were extremely variable. The possible reasons for this marked variability are discussed.

5. Two instances of mild local inflammatory reaction at the site of

injection were encountered. Both cleared spontaneously in three to four days time without abscess formation.

6. There were no allergic reactions to the injections in this entire series of 180 patients, who received a total of 696 injections.

7. No instances of acquired sensitivity to penicillin or the peanut oil-beeswax vehicle could be demonstrated by subsequent injection of these products two to four months later.

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SEDIMENTATION RATE IN ASTHMA

In Children

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In a previous paper (1), the results of the treatment of a group of 34 asthmatic children by irradiation of the lymphoid tissue of the nasopharynx with radon were reported. The ages of these patients varied from 2 to 14 years. All of them had suffered with frequent asthmatic attacks for at least 2 years prior to irradiation. This group included patients with all types of asthma: intrinsic and extrinsic, as well as instances of the mixed or unclassified type. Approximately one-half of the patients had had their tonsils and adenoids removed some time before the institution of the radon therapy.

During the course of this study, erythrocyte sedimentation rate determinations (Wintrobe technique) were done on 33 of the 34 patients treated in this manner. Determinations were made before the application of the radon therapy, during the course of the treatment, and after the treatment was completed. An attempt was made to perform at least two determinations on each patient under the same conditions. Also, before the radon therapy was instituted determinations were done on each patient, first, when the patient was entirely free of asthma, and, second, when the patient was having an asthmatic attack.

The sedimentation rates of each patient after having been treated with radon are shown in the following tables in relation to the outcome of the asthma. Corrected values read in one hour are reported. In each table the figures in *italics* represent the sedimentation rates taken during an asthmatic attack; the other figures denote an average of at least two determinations performed under the designated conditions.

The period of observation of these 33 patients, after the completion of the radon treatment, varied from 6 months to 4 years. The effect of the treatment on the course of the asthma was scored as follows:

(1) Completely relieved, when there was no recurrence of the asth-

TABLE I

Sedimentation Rates of Patients Who Were Completely Relieved of Their Asthma After Radon Therapy

PATIENT NO.	SEDIMENTATION RATES (MM. PER HOUR)		
	Before treatment	During treatment	After treatment
1	*18*–22	20	8
2	*26*–24	7	8
3	*36*–38	11	12
4	*42*–34	16	5
5	*26*–36	32	7
6	*46*–39	23	0
7	*26*–32	18	7
8	*21*–28	15	4
9	*22*–23	9	2
10	*26*–22	9	4
11	*27*–36	12	6
12	*11*–19	15	0
13	*28*–29	16	6
14	*42*–36	20	8
15	*38*–22	14	7
Average.....	*29*–28	16	6

TABLE II

Sedimentation Rates of Patients Who Were Markedly or Moderately Relieved of Their Asthma After Radon Therapy

PATIENT NO.	SEDIMENTATION RATES (MM. PER HOUR)		
	Before treatment	During treatment	After treatment
16	*9*–17	12	7
17	*11*–20	14	10
18	*17*–21	11	9
19	*11*–24	25	16
20	*38*–41	6	5
21	*29*–41	13	0
22	*11*–7	4	11
Average.....	*18*–24	12	8

matic attacks during the observation period and repeated physical examinations showed none of the findings typical of the asthmatic chest.

(2) Markedly relieved, when the patient had only an occasional mild attack of asthma in comparison to the frequent severe attacks prior to treatment.

(3) Moderately relieved, when the number of attacks and the severity of the symptoms became less than one-half.

(4) Failure, when the number of asthmatic attacks was only slightly reduced or the status remained the same, or the condition became worse.

TABLE III

Sedimentation Rates of Patients Whose Asthma Did Not Respond Favorably to Radon Therapy

PATIENT NO.	SEDIMENTATION RATES (MM. PER HOUR)		
	Before treatment	During treatment	After treatment
23	*2*– 4	5	8
24	*3*– 5	3	0
25	*0*– 1	0	0
26	*0*– 2	0	1
27	*9*– 1	9	0
28	*8*– 0	4	1
29	*4*– 5	9	0
30	*5*–12	16	10
31	*4*– 0	0	0
32	*7*– 2	3	1
33	*10*– 8	7	5
Average.....	*5*– 4	5	2

It will be noted that the sedimentation rate was essentially the same during both the asthmatic and the non-asthmatic states. Again, it will be observed that 21 of the 22 patients, whose asthma responded favorably to the radon therapy, had a high sedimentation rate before treatment. In all but one case these elevated sedimentation rates returned to normal after completion of the radon therapy. Of the 11 patients who failed to respond to the irradiation only one presented a slightly elevated rate before treatment.

COMMENT

These findings suggest, first, that the erythrocyte sedimentation rate determination may be a useful test in predicting which children

with asthma will be benefited by irradiation, and, second, that the sedimentation rate may serve to differentiate between infectious and non-infectious (allergic) asthma as has been pointed out previously by Coke (2) and Knott (3). This latter inference is further substantiated in this study by the fact that in all of the 22 cases whose asthma responded favorably to the treatment there was complete disappearance of the lymphoid tissue in the naso-pharynx, and again in all but one of these cases the sedimentation rate which was high before treatment returned to normal after the completion of the treatment.

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A HITHERTO UNRECOGNIZED TENDENCY TO THE DEVELOPMENT OF WIDESPREAD PULMONARY VASCULAR OBSTRUCTION IN PATIENTS WITH CONGENITAL PULMONARY STENOSIS (TETRALOGY OF FALLOT)

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The surgical treatment of congenital pulmonary stenosis recently devised by Blalock and Taussig (1) consists, as is now well known, in anastomosing a systemic artery (subclavian, innominate, carotid) to a pulmonary artery. By so increasing the amount of blood passing through the lungs, relief is afforded from the marked deficiency in the oxygenation of the blood that results from the pulmonary stenosis and from the shunting of unoxygenated blood from the right to the left ventricle through the ventricular septal defect that is usually present in these cases. The successful development of this operation has brought a large number of patients with the tetralogy of Fallot (congenital pulmonary stenosis, patent interventricular septum, dextroposition of the aorta, hypertrophy of the right ventricle) to this hospital for treatment. The condition of many of these patients at the time of their arrival at the hospital has been precarious. Some have died while awaiting operation. Others have been operated upon even though in a condition that made them extremely poor surgical risks, for the operation provided the only hope of their survival. Some deaths have represented the operative mortality to be expected in the development and performance of any operation of comparable seriousness, particularly in the presence of an abnormal cardiac mechanism. In the microscopical study of the tissues of two of the fatal cases there was encountered pulmonary vascular obstruction of a degree that could be of importance in contributing to the symptoms and, possibly, to the fatal outcome. It was regarded worthwhile, therefore, to examine a series of consecutive cases of the tetralogy of Fallot for the presence of these lesions, and they were found with a frequency that was altogether surprising (90 per cent of 21 cases).

The purpose of the present report is to call attention to this hitherto unrecognized tendency of these patients to develop widespread obstruction of the pulmonary vascular bed, for it is a matter that requires consideration in the interpretation of studies on the pathological physiology of the circulation in patients of this type.

The obstruction in question is the result of widespread focal thrombosis of pulmonary vessels of microscopic size. Both arteries and veins are involved, though in many instances it is impossible to decide whether the affected vessel is an artery or a vein, either because of the notorious similarity of the smaller pulmonary arterioles and venules (2), or because the wall of the affected vessel has been altered beyond recognition during the process of organization of the thrombus. Every stage of the process, from the formation of fresh thrombi to the organization and recanalization of older ones, is present (Figs. 1 to 10), and it is clear from the different ages of the thrombi in individual cases that the process is often a progressive one. Some of the older recanalized thrombi present an appearance suggesting minute cavernous angiomata (Figs. 4 and 5), but the abundant transition stages make it quite clear that lesions of this type are really the results of the recanalization of thrombi. This type of recanalization, leading to the formation of multiple, very wide channels separated by thin septa, is encountered only occasionally in the pulmonary vessels when thrombi undergo organization and recanalization in conditions other than pulmonary stenosis, and it is a very rare mode of recanalization of thrombi in systemic vessels. The mechanical conditions that favor its occurrence in cases of the tetralogy of Fallot are not clear.

It is especially to be emphasized that the thrombi in these cases tend to occur profusely throughout both lungs. In most of the cases in which they were present, they were found microscopically in the single routine section taken from each lung at autopsy. Further sections were made from each lobe of each lung in twelve of the cases, and the lesions were often found in the sections from each lobe. In some of the cases a remarkable mumber of vessels in the individual sections were involved. In one case (19506), as many as 91 cross sections of vessels containing organizing and organized thrombi were present in a single microscopic section measuring about 2 x 1 cm. The single section from each of the other lobes of the lungs in this case

contained, respectively, 35, 33, 19, and 14 obstructed vessels. The single section from each lobe of the lungs of case 19668 contained, respectively, 31, 18, 14, 10 and 4 obstructed vessels. The frequency with which the thrombi can be found in sections of only a few micra in thickness, taken at random from any part of any lobe of either lung, makes evident the profuseness of these obstructive lesions in most of the cases.

There arises the question why widespread thrombosis of the peripheral pulmonary vascular tree occurs with such frequency in patients of this type. It may be said at once that the thrombi are not simply results of the vascular operative procedure. While in some cases small thrombi may form at the operative site of anastomosis and become dislodged and swept as emboli into small branches of the pulmonary artery, it is to be emphasized that in most of these cases there is clear evidence that the thrombi occur independently of any operative procedure. In the first place, these widespread lesions are found in patients who have died while awaiting operation. In the second place, even in the operated cases thrombi are ordinarily present which are clearly much older than the survival time of the patient following operation. Completely organized, recanalized thrombi are found even in patients who died on the operating table, or within several hours after operation (see Table I). In cases 19561 and 19614, the only cases in this series in which the patients survived as long as 4½ days after operation, there are present fibrous, recanalized thrombi that are without question much older than the postoperative survival time.

Since it is perfectly clear that patients with the tetralogy of Fallot tend to develop spontaneous thrombi which obstruct the smaller pulmonary vessels, one may inquire whether these thrombi arise locally in the pulmonary vessels or represent small emboli from extra-pulmonary sites. There is no evidence that the arterial thrombi represent emboli, and it is altogether unlikely that they do. No thrombi were found in the hearts; and in cases of other types in which thrombi in the heart or systemic veins serve as the source of pulmonary emboli, no such extremely diffuse obstruction of minute pulmonary vessels as is present in these cases is encountered. It seems evident from the study of the present cases that patients with the tetralogy of Fallot

TABLE I

Tetralogy of Fallot. 21 Consecutive Autopsies

AUTOPSY NUMBER	SEX AGE	THROMBI IN PULMONARY VESSELS			REMARKS
		Organized canalized	Organizing	Fresh	
19444	M 10 mos.	0	0	+	Died 1 day after operation
19448	M 4 yrs.	+	+	+	Died 12 hours after operation
19466†	F 5½ mos.	+	+	0	No operation
19470†	F 16 yrs.	0	0	0	No operation
19480	F 7 mos.	0	0	+	No operation
19486*	M 21 mos.	+	+	0	Died 1½ days after operation
19506	M 5 yrs.	+	+	0	Died during operation
19521	M 4½ yrs.	0	0	+	Died 1½ days after operation
19526	M 4 yrs.	+	+	0	Died 8 hours after operation
19561	M 11 yrs.	+	0	0	Died 4½ days after operation
19579	M 3 yrs.	+	+	0	Died 2 days after operation
19614	F 11 yrs.	+	+	0	Died 4½ days after operation
19661	F 7 mos.	0	0	+	No operation
19668	F 2 yrs.	+	+	0	Died 1½ days after operation
19691	F 8 yrs.	+	+	0	Died 1 hour after operation
19697	F 3½ yrs.	0	0	+	Died 12 hours after operation
19717	F 20 yrs.	+	0	0	Died 3 hours after operation
19770	M 2 yrs.	+	+	0	Died 2 days after operation
19799	M 8 yrs.	+	+	0	Died during operation
19821	F 2½ mos.	0	0	0	Died during operation
19835	F 8 yrs.	+	0	0	Died during operation

* Pulmonary stenosis; interventricular septal defect; transposition of aorta.

† Capillary angioma present in one section.

have a marked tendency to develop widespread local thrombosis of the smaller pulmonary vessels, both arteries and veins. It may be stated that the study of the other viscera in these cases disclosed no such tendency to diffuse thrombosis as was found in the lungs.

There are two circumstances that may be expected to favor spontaneous thrombosis in the pulmonary tree in these patients. In the first place, the anoxaemia due to the inadequate pulmonary circulation causes the development of a compensatory polycythaemia, often of marked degree, and polycythaemia is recognized as a condition favorable to thrombosis, apparently because of the increased viscosity of the blood (cf. the formation of "marantic" thrombi in patients with increased viscosity of the blood due to dehydration). Spontaneous thrombosis of systemic vessels (e.g., cerebral vessels) is familiar in polycythaemia vera. How frequently widespread thrombosis of the smaller pulmonary vessels occurs in polycythaemia vera cannot be stated with confidence at present, for the lack of mention of thrombi in the pulmonary vascular bed, in the description of most of the cases in the literature, does not necessarily provide assurance that they were not present. The little thrombi in their organized recanalized state can easily be overlooked, as is evident from the fact that they have heretofore been overlooked in cases of the tetralogy of Fallot. A re-examination of the several cases of polycythaemia vera available in the files of this department has disclosed no thrombi in the sections of the lungs, but the number of cases is too small to be of value.

In addition to the factor of polycythaemia, patients with the tetralogy of Fallot are subject to another influence, not present in patients with polycythaemia vera, that can favor the development of thrombosis in the pulmonary vessels, namely, the inadequate pulmonary blood flow that results from the pulmonary stenosis. It is well know that circumstances that tend to slow the flow of blood in a vessel predispose to thrombosis of the vessel; and the greatly reduced amount of blood delivered to the pulmonary circulation in cases of pulmonary stenosis, with the consequent low pressure in the pulmonary artery, may be expected to reduce the rate of flow in the pulmonary vessels. Because of this additional factor favoring thrombosis in the pulmonary vascular bed, a case of pulmonary stenosis having the same degree of polycythaemia as a case of polycythaemia vera should be more likely to develop thrombosis of the pulmonary vessels.

Since patients with the tetralogy of Fallot suffer from a marked deficiency in the oxygenation of the blood due to the reduced flow of blood through the lungs, the presence of widespread thrombosis of the pulmonary vessels may well add to the difficulty of oxygenation. The marked interference with the oxygenation of the blood that results from the obstruction of microscopic pulmonary vessels in cases of Ayerza's disease is familiar. The presence of obstructive thrombi throughout the lungs may also affect the outcome of the surgical attempt to increase the pulmonary blood flow by anastomosing a large systemic artery to the pulmonary artery. Whether the increased peripheral resistance in the pulmonary circulation, in cases with widespread obstructive thrombosis of the pulmonary vascular bed, will place an additional burden upon the abnormal heart following the surgical therapeutic anastomosis, can hardly be answered on the basis of present information, for the activity of the normal compensatory mechanisms is at present unpredictable in these patients with a congenitally abnormal circulatory apparatus. The answers to these and to other questions provoked by the presence of the obstructive thrombi must await studies of pulmonary pressure and flow in the living patient, correlated with the degree of thrombotic obstruction found at autopsy. The observations recorded in the present paper serve principally to draw attention to a frequent complication that should be borne in mind in the interpretation of studies on the pathological physiology of patients with the tetralogy of Fallot.

SUMMARY

Widespread and progressive thrombosis of pulmonary vessels of microscopic size is a frequent occurrence in patients with congenital pulmonary stenosis (tetralogy of Fallot type). This condition was present in 90 per cent of twenty-one consecutive cases studied at autopsy. It is suggested that the predisposing factors are the increased viscosity of the blood resulting from the compensatory polycythaemia, and the reduced rate of flow in the pulmonary vessels resulting from the greatly diminished amount of blood delivered to the pulmonary vascular system. The possible clinical significance of this widespread obstruction to the pulmonary circulation is mentioned.

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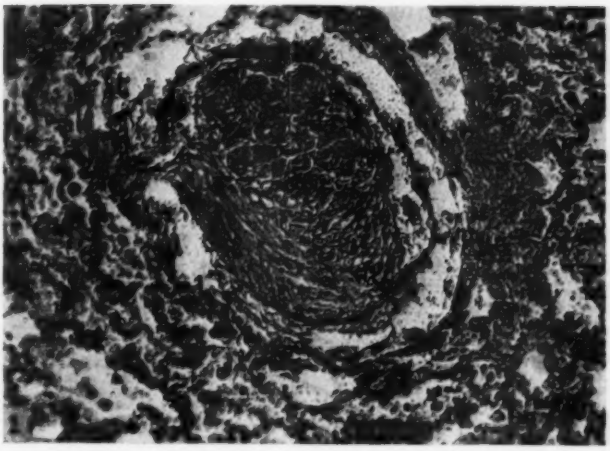
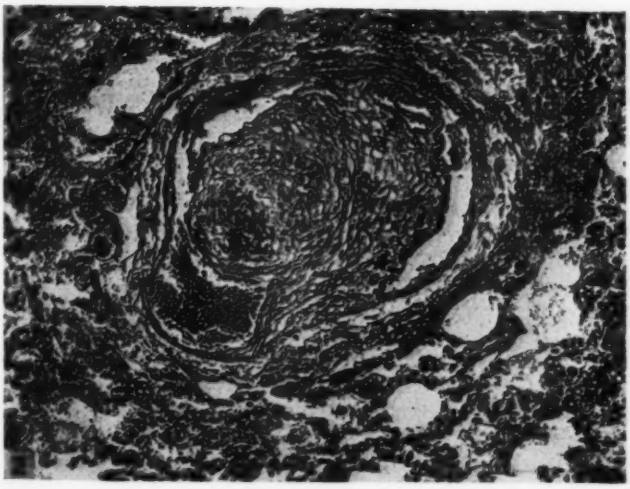
Explanation of Illustrations

(Photomicrographs by Miss Marjorie Jackson)

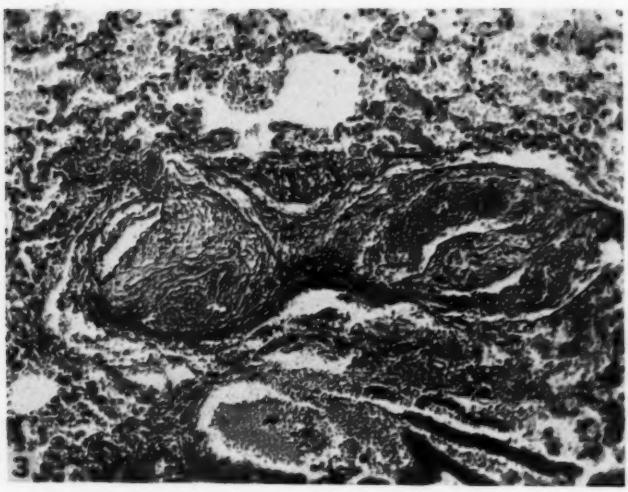
Figs. 1–5. Obstructed pulmonary vessels in Case 19668. Figs. 1 and 2 show thrombi still in the process of organization. Figs. 3, 4 and 5 illustrate older organized, recanalized thrombi.

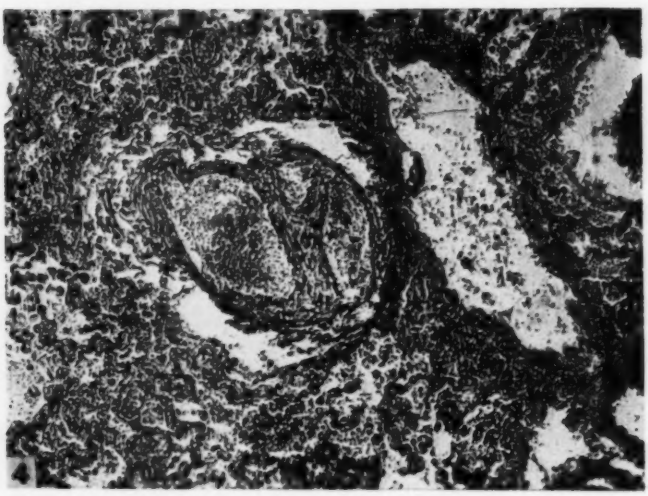
Figs. 6–10. Obstructed pulmonary vessels in Case 19506. The lower left portion of the thrombus in Fig. 6 is not yet organized; those in Figs. 7–10 are completely replaced by connective tissue and recanalized.



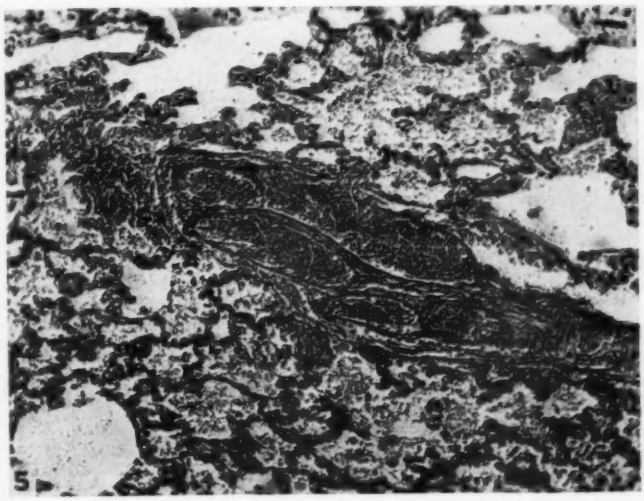


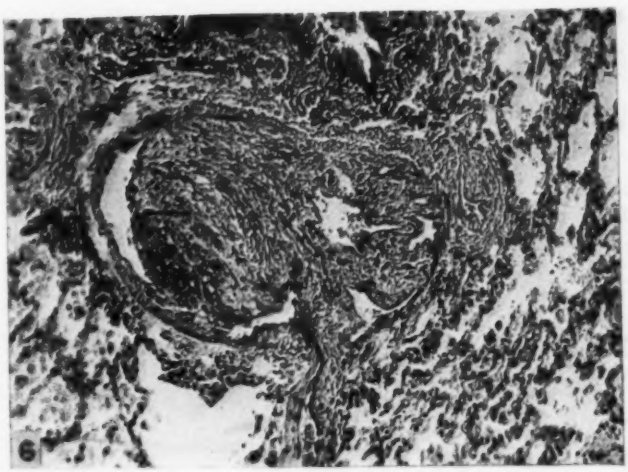
FIGS. 1–2



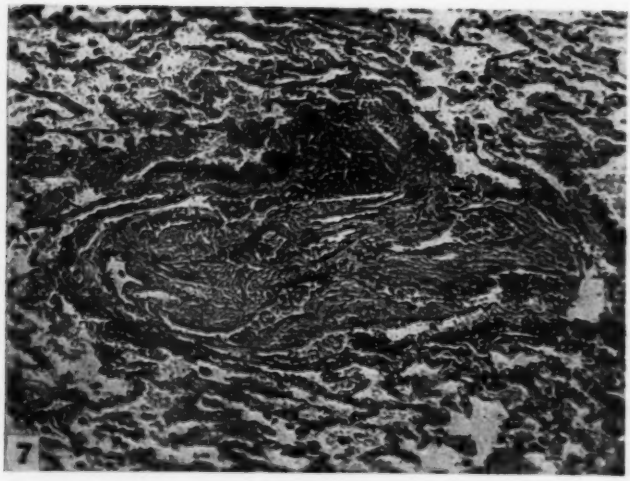


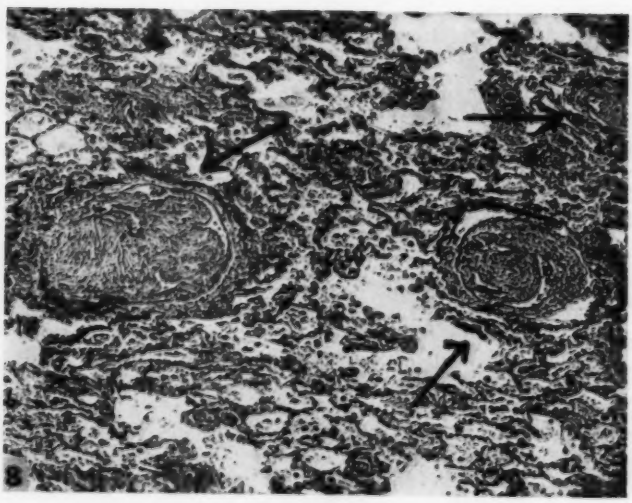
FIGS. 3–4



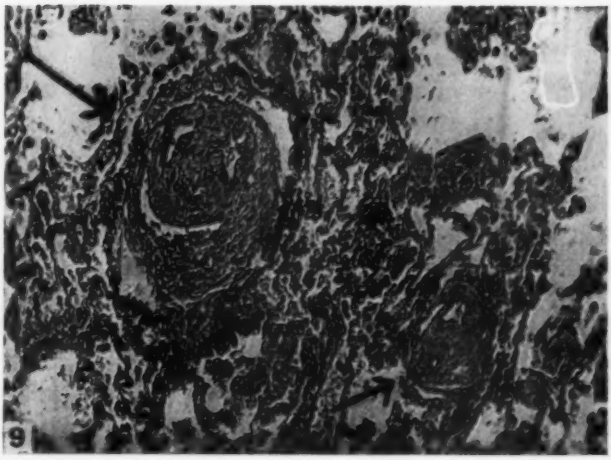


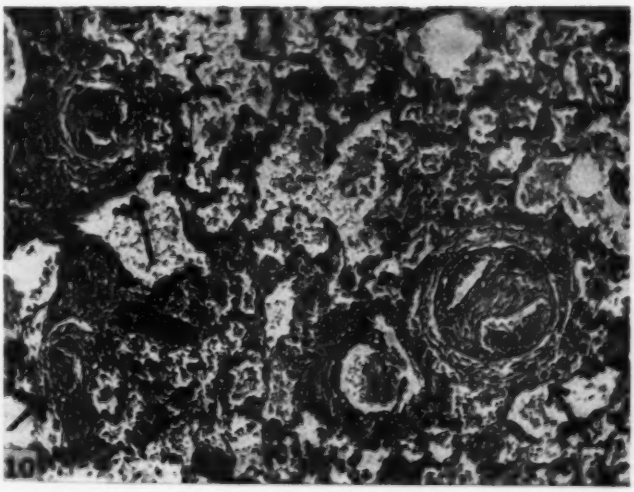
FIGS. 5–6





FIGS. 7–8





FIGS. 9–10

THE DOSAGE SCHEDULE OF PENICILLIN IN BACTERIAL INFECTIONS[1]

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Although it is established with certainty that the administration of adequate amounts of penicillin by a dosage schedule which maintains a more or less constant concentration of the drug in the blood for a certain time will cure many severe and serious infections, it is by no means established that this dosage schedule is the most satisfactory or the only effective one. It is not easy to define the criteria that should be used to determine the most satisfactory or most effective dosage schedule of a chemotherapeutic agent. The first requirement should be the cure of all cases of infection or attainment as near as possible of that ideal. In addition, the number and severity of toxic reactions and the discomfort and inconvenience to the patient must be considered. The cost of and requirement of the doctor's and nurse's time in administering the treatment schedule might then be taken into consideration.

The dosage schedule of penicillin in general use has been arranged on the basis of three unproven assumptions; namely, 1) that it is necessary to maintain, day and night, a more or less constant blood concentration of drug for effective therapy, 2) that *in vitro* results on the sensitivity of parasites to the drug can be transferred without modification to infections in man, and 3) that it is a crime to use more penicillin than is necessary for the cure of the infection. We can consider the evidence for the validity or non-validity of these assumptions.

The concept of a maintained blood concentration of drug for effective treatment appears to have been a transfer by analogy from therapy with the sulfanilamide derivatives. Due to the extremely rapid excretion of penicillin by the kidneys, it was at first thought necessary to give a continuous intravenous or intramuscular injection of the drug

[1] Presented as part of the Therapeutic-Pharmacological Conference, October 11, 1947.

to attain effective therapy. In fact, as recently as a month or so ago, we find the following statement in an article on penicillin: "The primary objective of penicillin therapy is the maintenance of therapeutic concentrations of the antibiotic in the body tissues" (1). One might have thought that the primary objective of any therapy was to cure the patient of his disease or to ameliorate disagreeable symptoms regardless of whether or not blood concentrations of drug are maintained.

Soon after the introduction of penicillin, the continuous intravenous or intramuscular drip was abandoned in favor of single injections at 2 to 4 hour intervals. This does not maintain a constant blood concentration. Due to the inconvenience of this schedule to both patient and attendants, various methods have been tried to prolong the blood concentrations that result from an injection of penicillin. These methods have attempted to decrease the rate either of its absorption or of its excretion. The most efficient method so far discovered of delaying absorption is the use of intramuscular penicillin in peanut oil-beeswax instead of in water. This slowing of absorption decreases the number of injections which have to be given in order to maintain a more or less constant blood concentration. The most satisfactory method of decreasing excretion is by the simultaneous administration of caronamide. This drug has not, however, been used primarily to decrease the interval between injections of aqueous penicillin, but has been used to decrease the amount of penicillin necessary for therapy. Its advantage is apparently a purely economic one of decreasing the cost of treatment. Where large amounts of penicillin are required in certain cases of infection, i.e., subacute bacterial endocarditis or where oral therapy is used, this may be an important factor. A marked disadvantage of caronamide is the very large daily dose of this drug which must be given.

As early as 1944, Tillett (2, 3) and coworkers reported results on the treatment of pneumococcic pneumonia which appear to show that the damaging effects of penicillin on invasive pneumococci restrained their regrowth for a considerable period after blood concentrations ceased to be measurable. They also state that when an interval of 12–16 hours was allowed to elapse between daily courses of injections the results were just as satisfactory as when the injections were maintained throughout the twenty-four hours. The number of cases studied

was small, but also the dosage of penicillin was small according to present standards. It may also be mentioned that in an article in 1944 on the "Clinical Use of Penicillin" Dawson and Hobby (4) state, "It should also be mentioned that little is as yet known concerning the minimal effective concentration for various types of infection. Such experimental work as has been done has been based on the assumption that effective concentrations should be constantly maintained in the circulating blood as is the custom in sulfonamide therapy. Certain facts suggest, however, that this may not always be necessary." In another article by McDermott et al (5) appearing in 1945, the following statement occurs, "There is also reason to believe from clinical experience and from certain of the *in vitro* experiments that this prolonged maintenance of an effective level need not be absolutely continuous."

We shall now discuss experiments on the treatment of bacterial infections in animals which may be of assistance in deciding dosage schedules of penicillin. It is of importance to note that a single dose of penicillin X will cure mice infected with a streptococcus (6), a phenomenon which cannot be duplicated with a sulfonamide. The experiments of Jawetz (7), published in January, 1946, are of significance. These appear to show that the effects of penicillin on the bacterial population in a streptococcus infection in the mouse last much longer than the measurable blood concentrations. The latter persisted for only about one hour after injection of the drug, while depression of bacterial population continued for eight hours or longer. It is to be noted that these experiments were done with a crude penicillin preparation of unknown composition.

Zubrod (8) in our laboratory has investigated the relative efficacy of different dosage schedules of penicillin in a β-hemolytic streptococcus infection of mice. Two samples of crystalline penicillin G, accurately documented and of high purity, were used. He found that, in treatment with multiple doses of aqueous penicillin, survival depends more on the total dose administered than on the number of fractions into which the total dose is divided. Although the blood concentration of the drug in mice is not measurable after about one hour, his experiments show clearly that nothing is gained by giving penicillin more often than once in twenty-four hours. The responses to a single dose cannot

be compared with those to multiple dose regimens because the dosage-response curves are not parallel—the single dose gives a much flatter type of curve, i.e., for each increment in dosage there is only a small gain in the number of mice surviving. These experiments by Zubrod give no evidence for the necessity of a maintained blood concentration of drug for effective therapy, but, on the contrary, suggest that the interval between doses of an aqueous solution of penicillin may be markedly increased and treatment still be highly effective in human bacterial infections.

A fact that must be considered in assessing the value of animal experiments on dosage schedules is that conclusions are based on calculated median curative doses, whereas we are more concerned with doses producing the maximum percentage of cures in human disease. The determination of doses producing effects in proportions close to one hundred per cent is difficult in that enormous numbers of animals are necessary to avoid a large error. In addition, one must recognize the hazard of transferring results obtained in the mouse to man without detailed knowledge of the pharmacology of the drug and the course of the experimental infection.

We can turn now to the second assumption upon which the dosage schedule of penicillin has been based. From a consideration of the mechanism of action of many chemotherapeutic agents, it seems unlikely that results obtained *in vitro* can be transferred to *in vivo* conditions with penicillin. However, one still finds this *in vitro* argument used for setting up a dosage schedule of penicillin (9). Some results reported by MacLeod (10) on pneumococcus infections in mice are evidence against the validity of transferring *in vitro* results to *in vivo* conditions. Infection was produced with strains of types I and III which had the same virulence for mice and the same sensitivity to penicillin *in vitro*. Infection with type I was much more easily cured in the mouse than was infection with type III.

The idea which is expressed in many publications, of defining the minimum dose of penicillin necessary for effective treatment and speaking of penicillin given in excess of this as so much waste, stems from the early days when the drug was so scarce that Florey recovered it from the urine of his patients. Also, lack of knowledge of the potential toxicity of the new drug led to conservatism in dosage. In order to

cure the maximum number of patients, dosage must be greatly in excess of the minimum curative dose for many individuals. Moreover, with an abundance of penicillin and with its purification to a point where such toxicity as is found is completely independent of dosage, waste becomes purely an economic matter. This economic factor is becoming of less and less importance.

In view of what has been stated above, it appears that there is a persistent antiparasitic effect of penicillin long after its disappearance from the blood. Hence, it appears probable that the maintenance of a more or less constant blood concentration is unnecessary for efficient therapy in the human. This means that it should be possible with aqueous penicillin given in three, two, or even one injection per day to accomplish satisfactory therapy. Probably very little increase in total daily dosage would be necessary. The advantage of such a dosage schedule over those where injections are given every two to four hours, or where injections of the peanut oil-beeswax preparation are used, appears obvious. Whether or not such dosage schedules can be used in all infections must be determined by careful, controlled clinical trials.

It may be mentioned in conclusion that in several clinics penicillin has been used successfully in aqueous solution with only two or three injections per day. This is in agreement with the argument presented above.

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PROCEEDINGS OF THE MEETING OF THE JOHNS HOPKINS MEDICAL SOCIETY

Held in Hurd Hall, November 10, 1947

Reduction of Intussusception by Barium Enema: Clinical and Experimental Study. Dr. Mark M. Ravitch and Robert M. McCune, Jr. (Department of Surgery, Johns Hopkins Hospital).

The treatment of intussusception in infants and children by hydrostatic pressure has been routinely employed in reputable clinics in Europe and Australia for some 75 years. The results in terms of morbidity and mortality have from the first been superior to those reported from clinics using operation alone. In the Johns Hopkins Hospital since 1939 there have been 27 patients with intussusception who were treated primarily by barium enema. There were no deaths in this group and the average hospital stay was 9.2 days. During the same period of time there were 21 patients whose intussusceptions were treated primarily by operation with 5 deaths, or a 24% mortality. The living patients in this group had an average hospital stay of 32.4 days and a very much higher morbidity than the group treated by enema. It is fairly clear from the numerous reports of large numbers of cases treated by hydrostatic pressure that, with a pressure of 3 feet and without manipulation of the intestine through the abdominal wall, the bowel will not rupture and non-viable bowel will not be reduced.

An experimental method is described for the production of intussusceptions in dogs. Reduction of such intussusceptions by hydrostatic pressure of 3 feet confirms the clinical impression that non-viable bowel will not be reduced by a pressure of 3 feet. The histopathological features of intussusception are described. Bacteriological study showed several varieties of pathogenic organisms on the serosal surface of intussusceptions containing viable bowel.

Barium enema reduction of intussusceptions in infants and children by a surgeon, and in a hospital, is recommended as the primary treatment for the condition.

Dr. Alfred Blalock: Up to the time that Dr. Ravitch began this work, I had the same opinion in regard to the nonoperative treatment of intussusception as I had held about the nonoperative treatment of irreducible herniae. I remember so distinctly the views of a postgraduate student some years ago who stated that it was never necessary to operate upon irreducible herniae. In reply to a question as to how he treated this condition, he stated that he suspended his patients by their heels and gave them big dosages of apomorphine. According to this student, this resulted in vomiting and in a reduction of the hernia. It is obvious that this student was unwise in his choice of therapy, and I rather felt this way about the nonoperative treatment of intussusception until Dr. Ravitch convinced me of the safety of the procedure in his hands. I think that anyone using the method which he has described should realize that it is not devoid of danger in patients

who have an impairment of the blood supply of the intussuscepted part. Certainly the results which Dr. Ravitch has obtained are excellent, and I wish to congratulate him on this study and on the manner in which he has presented it.

Dr. Mark M. Ravitch: I think we would be perfectly satisfied if all those who are uncertain of their ability to diagnose the completeness of reduction would treat every case with enema and then routinely make a McBurney incision to confirm the completeness of the reduction and to see the condition of the bowel. I think the mistaken diagnosis of complete reduction would certainly be the greatest danger. Unless the bowel is manipulated or unless excessive pressure is used there appears to be very little danger of rupture.

Studies on the Diuretic Action of Diacetylformoguanamine in Dogs. DR. ELLIOT V. NEWMAN, DR. JOHN FRANKLIN, and DR. JACQUES GENEST. (Department of Medicine, Johns Hopkins Hospital).

From a large series of chemically related compounds Lipshitz selected melamine, adenine, and formoguanamine as having high diuretic activity by a test on rats.

The purpose of our study was to determine the mechanism of action of diacetylformoguanamine (DAFG) in dogs.

Adult female dogs weighing 13 to 18 kilograms were kept on a constant weighed diet of known composition. Total 24 hour collections were made of urine which was analyzed for sodium, chloride and potassium content. The dogs were weighed daily.

The results showed that when 0.5 gram of DAFG was given orally for one day with water provided ad lib, there was a rise in urine output of from three to five fold the control value. Intake of water usually kept pace with the output. There was little or no increase in the total 24 hour amount of sodium, chloride, or potassium in the urine and no weight loss.

When water was restricted to a normal volume (determined from the intake during the control periods), or when water intake occasionally did not quite keep pace with the output, there was a marked diuresis of from two to four times the control output of water and there was a marked increase in sodium and chloride output, and a moderate increase in potassium output. The dogs lost as much as one kilogram in weight in one day.

Administration of one to one and a half grams of DAFG for one day frequently caused a diuresis lasting two to four days, diminishing each day after the large initial diuresis. A post diuretic retention of sodium, chloride and potassium was marked after the first day of diuresis whenever water was restricted.

Administration of pitressin in large doses with DAFG did not alter the magnitude of the diuresis obtained.

Crystalluria was noted occasionally in the catheterized urine specimen the morning after DAFG administration. The crystals were brown, oval or round, with coarse concentric rings and fine lines radiating from the center to the periphery. No hematuria nor albuminuria were noted. These crystals were found

only after careful routine search in morning catheter specimens which were centrifuged.

Administration orally of one gram a day of DAFG for five days caused, after the third day, a progressive drop in the creatinine clearance, para-amino hippuric acid clearance and Tm to twenty per cent of control normal values.

There was a rise in urea nitrogen. No suppression of urine output occurred at any time, a diuresis being sustained throughout the period of administration. Two weeks after discontinuing DAFG administration, all renal function tests mentioned above had returned to normal.

Another dog was sacrificed after five days of DAFG administration, when there was evidence of suppression of renal function tests but no suppression of urine output. Histological examination of the kidneys revealed a few of the crystals described above, with areas of dilated tubules and areas of normal kidney. The crystals were impacted in the tubular lumen.

Dr. Samuel P. Asper, Jr.: Dr. Newman, using diacetylformoguanamine, has confirmed the studies of Dr. Lindley on the diuretic action of these related compounds, and has given us a very good idea as to the mechanism of their action. In Boston, Dr. Myers, Dr. Williams, and I were interested in formoguanamine, and we made a few clinical observations on the use of this compound which is similar to the compound Dr. Newman just described. In six normal subjects and in nine patients with edema we were unable to obtain any significant diuresis. At times it seemed a slight diuresis occurred, but the results were neither consistent nor reproducible, and, furthermore, were of no therapeutic significance. In oral doses of 0.2 to 3.0 grams, we always obtained crystalluria with formoguanamine. These crystals vary in size, are visible in the urine to the naked eye, microscopically are green-brown, have radial striations and concentric markings. Under polarized light they are doubly refractile. In one patient, 1.6 grams of formoguanamine was administered on two successive days. There was no significant rise in the urine output over a control volume. There was no change in weight. On another occasion, 3.0 grams of formoguanamine was administered. Crystalluria became marked and the urine output fell to 200 cc. for two days thereafter. The urine sediment showed numerous red cells, white cells, occasional hyaline casts, and some of these casts had crystals attached to their surfaces. We were disappointed with the clinical experience with formoguanamine, and thought perhaps that there might be some different metabolic fate of formoguanamine in human beings as compared to that in animals—rats and dogs—that Dr. Lindley used.

Dr. Arnold R. Rich: I don't know whether Dr. Newman meant to imply that I concurred in the opinion that the kidneys of the treated dogs were normal. Certainly I would say that the picture of the first one looked very decidedly abnormal to me. The tubules were tremendously dilated and some were plugged with crystals. In the second lantern slide, one of the tubules seemed to be full of pus cells.

Dr. Elliot V. Newman: I should say that there have been other clinical studies which are rather conflicting and difficult to understand. There is at least one

report published, and maybe others, which say that formoguanamine is an effective diuretic, and I understand it is being widely used in some places. This is perhaps quite dangerous, as Dr. Asper has pointed out, and unless one looks carefully for crystalluria and other manifestations of renal damage one may not find it. Regarding the histological sections, I should have said that the area shown in the lantern slide, with the crystals in the tubular lumen, was abnormal as Dr. Rich has pointed out, but that numerous areas in other parts of the kidney were perfectly normal. The main pathological lesion seems to be one of focal obstruction due to crystals impacted in the tubules.

The Roentgenologic Diagnosis of Tuberculosis. DR. RUSSELL H. MORGAN. (Department of Surgery, Johns Hopkins Hospital.)

Since the introduction of mass radiographic methods for the early detection of tuberculosis, considerable concern has been raised as to the efficiency with which these methods discover tuberculosis. Within recent years, two comprehensive investigations have been carried out to determine this efficiency. One method employed a system wherein comparative surveys of the various methods were studied. The other method followed quantitative evaluation of the physical factors controlling the diagnostic quality of x-ray films of various sizes. Both these methods have proven conclusively that all the mass radiographic methods are as efficient as regular 14 x 17″ films in the early detection of tuberculosis. It therefore can be confidently stated that the concern which has been felt regarding the usefulness of mass radiographic methods is unfounded and that these methods can be used without question in studying such groups as hospital employees and university student and faculty members.

Dr. Moses S. Shiling: I have been reading small chest films now for several years, and I would like Dr. Morgan to comment on the speed at which these small films can be read. I often hesitate to admit how fast one can read them. Not infrequently, 1000 to 1200 small films can be read in one hour without sacrificing accuracy.

It is difficult to understand how one expert can read a film as far advanced and another read the same film as negative. I can visualize several situations where this difficulty might arise in interpreting small films. One is the case of the large shelled-out cavity involving only a rim of tissue adjacent to the pleura. In this condition one might miss the complete absence of lung markings. Another similar situation could arise in the interpretation of cavities occurring in the so-called hilar regions of the lungs. These may well be picked up by some and missed by others.

Dr. A. McGehee Harvey: I would like to ask what the variations were when the same reader read the films on successive days.

Dr. Russell H. Morgan: In regard to Dr. Shiling's question about the speed of reading, some experimental work on evaluating diagnostic efficiency has been done as part of the Veterans Administration study, and it was apparent that the subjective error of reading is not very closely related to the speed of reading. Those

who read at rates of upwards of 800, 900, and 1000 films an hour did apparently just as well as those who read at much slower rates, such as 100 or 150 films an hour.

Now as far as the question of missing far advanced tuberculosis is concerned, sometimes I think that that can be explained upon differences of designation. Frequently a process may be far advanced from the standpoint of its extent but looks so fibrous that the reader, without any bacteriological knowledge, diagnoses it as negative for tuberculosis, whereas the more careful reader a few minutes later will see the same picture and wisely, since he knows nothing of the bacteriological process involved because the film has no history attached to it, diagnoses it as a far advanced case. I think there is a good deal of that sort of thing in this reading. It is a subjective type of error, regardless of what you want to call it.

Now as far as readers who read the films twice are concerned, strangely enough there was as much discrepancy between two readings by the same reader as that which occurred with a number of readers reading the films once. In other words, if Dr. Smith (there wasn't any Dr. Smith in the study) read the series of cases one day, and then reread them the next week, his discrepancy from one week to the next was in the order of about 15%, the same as the discrepancy between five different readers reading films simultaneously. This subjective error is apparently a failing of human beings. I can't be too concerned with it. I am sure that if the records in the past year were inspected in our department and checked with final pathological interpretations on those cases, many films which I have read as negative would actually reveal pathological changes in many instances. I can't get too disturbed about this because these discrepancies are bound to occur. There are a great number of causes for them of course—fatigue of reading, the pressure of other activities, an inadequate amount of clinical information. All of these may throw us off the track or not lend sufficient emphasis to certain things that we would have noted if we had been tipped off ahead of time. Those are the things that are going to cause error. We do our best to hit the mark as often as possible; at least we keep our eyes as close to it as we can. Furthermore, I suspect that if it were possible to analyze carefully the clinical cases that come on the floor of this hospital, the best of our clinical personnel would make discrepancies in a certain number of cases. I am sure it is not a failing of radiologists and chest specialists alone.

Dr. Arnold R. Rich: I am sure that we all have great admiration for Dr. Morgan's simple and sensible method of evaluating the different types of film. While it is clearly a more objective method than has heretofore been used, I would like to ask Dr. Morgan how much subjectivity enters into it. At a given distance, for example, did it happen that one man would say, "I can't see any lesion", and then, after hearing the description of the lesion by the other two, would become able to distinguish it himself? Also, was there any attempt made by three men together to evaluate a group of films by the same method, without knowing in advance whether lesions were present or not? I am just interested in knowing how much of the process was subjective.

Dr. Morgan: I am sure that there is some subjectivity that comes into the picture. However, since we knew that the lesion was actually there, psychological factors involving competition among the various readers did not immediately come into play. I will say one or two words in regard to your first question—"What happens when the opinions vary; did the situation occur when two readers saw the lesion and a third did not?" That occurred not infrequently, as you would expect statistically, and whenever it did occur we abided by the majority rule. One interesting thing that came up in that connection was this: we observed, let us say, a group of films of moderately advanced cases at 10 meters. If a case came up in which one of us could not see the lesion and the other two could, we found that if the non-seeing reader went a half a meter closer to the film he could then usually pick up the lesion. Reversely, if the two went a half a meter farther back they might fail to see the lesion. The threshold between seeing and not seeing was fairly critical. In other words, in spite of the suggestion that this is not an entirely objective method, I think that it is fairly close to being one. One thing that I might point out, if there are any statisticians present, I think that we have been successful in showing that, in by far the largest percentage of instances, all of the methods not only are able to pick up the lesions that we studied but are likely to pick up lesions much finer than those we studied. From the charts you noticed that the ability of our 14 x 17 film to record detail was a great deal better than that necessary to pick out the finest of the processes. The shoulder of the curve was a long way away from the resolving power of the film. I think, as far as the diagnosis of tuberculosis is concerned, x-ray procedures are on pretty sound ground so long as the interpreters exercise the best possible diligence in observing the films. One other important thing is that the observers should not try to evaluate the activity of the lesion as soon as they detect the pathology. As soon as the readers attempted to do this in the Veterans Administration study, the discrepancy varied markedly. It is not surprising that this situation exists because x-ray methods are not histological methods, nor bacteriological methods, and the evaluation of the accurate status of the lesion must be determined by those methods rather than by x-ray. X-rays have done an admirable job in detecting the pathology. I think we should be appreciative of that fact. There are other excellent methods by which activity may be evaluated.

PROCEEDINGS OF THE MEETING OF THE JOHNS HOPKINS MEDICAL SOCIETY

Held in Hurd Hall, December 8, 1947

Diagnostic and Therapeutic Technique Used in Hearing Rehabilitation. Dr. William G. Hardy. (Department of Otolaryngology, Johns Hopkins Hospital.)

The incidence of hearing disability is analyzed, and emphasis is placed upon the fact that only a small proportion of the affected group has as yet received adequate treatment. The recent growth of the field of audiology is discussed, and pertinent data, relating to clinical developments and psycho-acoustic research, are outlined.

The problems and methods of the field are given concrete demonstration by an analysis of the Navy's program of aural rehabilitation established in World War II. In connection with this program, lantern slides of physical facilities and certain research summaries are presented. The point is made that the clinical experience gained during wartime in the processing by the Army and the Navy of 16,000 patients with a handicapping hearing loss, offers rich resources for the development of similar clinical services for approximately 8,000,000 civilians with similar problems. (Of this patient-load of 16,000, the Naval center has handled 5,000 active-service personnel and veterans.)

On the basis of this wartime experience, certain pertinent generalizations are adduced:

1. Hearing rehabilitation is largely concerned with the treatment of a communicative disorder caused by hearing disability.
2. This disorder is psycho-social in nature and scope.
3. Contrary to general belief, the purchase of a hearing aid is by no means a sufficient answer to the needs of the hard-of-hearing person.
4. Adequate hearing rehabilitation must be organized in terms of three basic steps:
    a. Thorough clinical diagnosis, employing objective measurements of auditory acuity and emphasizing the relationship of the communicative disorder to the behavior of the individual.
    b. Careful selection of the hearing aid most appropriate to the individual's needs by means of adequate objective and subjective measurements and evaluations.
    c. A retraining course in communicative skills, including auditory retraining, speech reading, speech training and mental hygiene,—the entire course gauged in terms of each individual's specific needs.

Certain special problems relating to psychogenic involvements and the development of language in children are outlined, and the relationship of hearing rehabilitation to the conservation of hearing is mentioned.

Pertinent research needs involving otology, psychology, physics, electronics and psycho-acoustics are suggested.

Dr. Stacy R. Guild: Besides congratulating Dr. Hardy on his report of the work in which he participated during the war, I wish to point out one aspect of the application of rehabilitation techniques to civilians which Dr. Hardy did not state. The broad application of this program will reduce the cost to the taxpayers of educating hard-of-hearing children. The cost of preventive measures for deafness and of fitting children with hearing aids will not be nearly so great as the cost of special educational procedures, special schools for the deaf, special teachers for the deaf, etc. I believe that Dr. Hardy's cooperation with the Department of Pediatrics and with city and state-wide agencies will more than make up its cost. We can call it preventive medicine if we wish.

Dr. William G. Hardy: I can supply one figure with which I am acquainted. Among several states on the Atlantic seaboard at least $1300. to $1800. per individual is spent annually among congenitally deafened children. I don't know what percentage of these children need not be in that group but it is probably a significant percentage.

Dr. Alan M. Chesney: I would like to speak for a minute from the standpoint of the guinea pig. I was very much interested, naturally, in Dr. Hardy's paper, and especially in his work which is starting here. I think it appropriate to tell this audience that the opportunity to start this work was made possible through the generosity of several of Dr. Crowe's patients, one of whom is himself obliged to wear a hearing aid.

It is quite true that the hearing aid of today is much better than it used to be. The old carbon-filament type of instrument was very unsatisfactory, but with the introduction of the radio amplification tube the whole picture changed. The only difficulty now is that so many improvements are being made and they are so expensive that you can't get a new model each year without spending a great deal of money. Maybe that will be straightened out as time goes on.

There is one point I would like to bring up that should be a matter of interest to all of us who are in the position of being medical teachers or medical students, and that is the question of the development of the amplifying stethoscope. I have watched its development with some interest, and I listened last year with the aid of an amplifying stethoscope to chests and hearts for a brief period and was amazed at what I could hear. I am satisfied that I heard things I didn't hear when I was a student, and I wouldn't be at all surprised if the development of amplifying stethoscopes reaches the point where all physicians starting out will want to have such a stethoscope and not wish to make use of the relatively inferior instrument which medical people have been using for a long time. If I were a youngster going into medicine now, I would keep my eye on that aspect of physical diagnosis. I rather think that a physician, with an amplifying stethoscope, may be able to hear things which his colleagues can't hear and which are really there and not imaginary.

It is very nice to have this work starting here under Dr. Hardy's supervision.

Dr. John C. Whitehorn: I would like to make a very brief comment on one angle of this work as related to the field of psychiatry. In recent years we have stressed very much the importance of taking into account factors of human nature in the adjustment many people have to make to medical and surgical conditions. I am looking forward with much excitement and pleasure to participating and sharing in the results of Dr. Hardy's work here, as he has indicated tonight that his work has necessitated a very real taking into account of people's attitudes and the emotional stress which may hinder their best use of the apparatus available. I think we in psychiatry have an opportunity to learn quite a lot about normal human nature through the chance that Dr. Hardy will give us to have a look-in on his enterprise.

A Physiological Basis for Nervous Dysfunction. Dr. W. Horsley Gantt. (Department of Psychiatry, Johns Hopkins Hospital.)

The organism tends to preserve itself and to adapt both individually and as a race, a function which has been well elaborated in Darwin's evolution and Cannon's homeostasis. This tendency of the organism to maintain an equilibrium through the higher nervous activity has been clearly demonstrated by Pavlov in his concept of the conditional reflex—a mechanism expressive of the individual's ability to adapt to the changes in its external environment.

A comparative study in my laboratory of the cardiac conditional reflex—the existence of which has been established here—with the salivary and the motor conditional reflexes ("crs") brings to light another and opposite basic characteristic of the organism, viz. the tendency to maladaptation or nervous dysfunction. The cardiac cr is *par excellence* a measure of emotional function. A comparison between the cardiac crs, with the secretory and with the somatic function of skeletal muscular movements, reveal two elements of dysfunction: 1) excessive cardiac reactions acquired through the experience of the individual, out of proportion to the biological needs, and 2) a persistence of these acquired cardiac crs after the more superficial crs have disappeared because of a change in the situation—a persistence which represents a failure of adaptation in the emotional nature, although there has been an adaptation in the more external aspects. We thus have to admit a basic function inherent in the organism making for maladaptation. A recognition of this dysfunction explains much of our normal nervous imbalance as well as the more extreme examples—neuroses and psychoses.

Dr. John C. Whitehorn: Those of us who have the responsibility of working clinically with people whose emotional functions are disturbed learn through difficult and complicated clinical experience the importance of those persisting maladaptive emotional tendencies which keep on acting in a person even when he knows better, so to speak—a situation strikingly analogous to that of dogs, which Dr. Gantt has spoken of, whose hearts have a conditional reaction different from that of their salivary glands and motor apparatus. We develop a way of thinking and talking about these matters in terms of emotional conditioning which is inter-

nalized and persistent. It may well be that through the type of experimentation which Dr. Gantt pursues diligently, we may be granted a more intimate view of the physiology underlying these persistent maladaptive emotional or cardiac patterns. This would be of very great importance for the understanding of persisting anxiety reactions. I can't stop without yielding to the temptation to speak of a further complication clinically which exists on top of this matter, namely that we do not infrequently deal with people who have found a solution, apparently not available to some of these dogs, whereby they become immune in a pathological way to the upsetting implications of some of the situations, but do this by delusion formation or by other devices which aren't very well adaptive either, so that the clinician oftentimes considers it a triumph therapeutically to get the patient to a state where his heart will respond. Sometimes he will have some moderately appropriate reactions and then there is a possibility that he can be helped still further.

Dr. Harry A. Teitelbaum: Since the process of extinction as described by Dr. Gantt apparently relieves animals, including man, of the necessity of responding to stimuli which are no longer of biological value, it must play a very important role in adaptive mechanisms. This presents the possibility of an interesting thesis. Whether Dr. Gantt's observations corroborate this thesis or not, it is impossible to say at this time. About all we can say about it this evening is that it seems that the more highly specialized tissues like the salivary glands and striated muscle tend to extinguish conditioned responses more readily than the less specialized tissues like the heart and the lungs which are more essential for the vitality of the animal. Can one postulate that the more specialized tissues are more highly sensitive and become conditioned more readily, and therefore play a more important role in adapting an animal, than the less specialized tissues in which the conditional responses are not extinguished and persist perversely and clinically in man? Referring to anxiety or emotional disturbances, it is possible that these less specialized tissues are less likely to extinguish their conditioned responses, and therefore are less adaptive. I wonder if Dr. Gantt could expound on these thoughts and tell us whether it is a tenable thesis or not.

Dr. W. Horsley Gantt: I am glad to have Dr. Whitehorn's and Dr. Teitelbaum's comments and the amplifications. I don't know that I can say anything especially that would illuminate the matter further than they have already done. I just want to add that necessarily I have condensed and, to a considerable extent, oversimplified this in order to give you a clearer idea than would have been done if I had put in a great deal of more complex material, and I offer it as a hypothesis which future work may confirm or reject.

Chemotherapy of Tuberculosis in Children. Dr. Edith M. Lincoln. (Department of Pediatrics, New York University.)

A brief report of results with promizole includes the failure to cure five children with tuberculous meningitis with this drug, and our comparatively good results in

acute generalized miliary tuberculosis. Seven cases of the latter were treated for more than a month, and five of these are now free from x-ray evidence of miliary tuberculosis one to three years after the original diagnosis.

Streptomycin has been used in various forms of extrapulmonary tuberculosis with results similar to those obtained by other investigators. It has proven particularly valuable in curing pharyngeal and endobronchial tuberculosis and in promoting closure of draining sinuses. Streptomycin has produced rapid improvement in pulmonary tuberculosis of the so-called reinfection type but no cures. Patients with tuberculous meningitis were not treated with streptomycin alone, but seven cases were treated with streptomycin together with promizole. Six of these have survived for four to eight months, are normal mentally, and have no evidence of permanent neurologic damage. These cases have not been under observation for a sufficient length of time to be reported as cures. This is merely a preliminary report on combined therapy of tuberculous meningitis with streptomycin and promizole.

Dr. E. K. Marshall: The first attempts to use chemotherapy for tuberculosis were started in 1899 by Cornet, who treated guinea pigs with mercuric chloride. I think one only has to listen to what Dr. Lincoln has told us to realize what enormous advances have taken place in the last decade, in spite of experiments with thousands of compounds of all types which have been done in the past on experimental and human tuberculosis. There seems little doubt that a new era in the chemotherapy of tuberculosis has dawned. Dr. Lincoln's observation, that very prolonged treatment with promizole is necessary for a good chemotherapeutic effect, is very important because one may be led astray if treatment is not continued long enough. This has recently been found by Dr. Feldman at the Mayo Clinic in an investigation with p-aminosalicylic acid on tuberculosis in the guinea pig. The first experiment with this substance showed absolutely no effect. Here treatment lasted for only forty-five days. When the experiment was repeated and treatment was continued for one hundred and fifteen days, a markedly favorable chemotherapeutic effect was obtained. I should also like to comment on Dr. Lincoln's very interesting and important results with combined therapy (streptomycin plus promizole) in tuberculous meningitis. Possibly this is carrying us back to the antiquated method of shotgun prescriptions. However, there is definite evidence on experimental infections in animals in favor of combined therapy. Dr. Lincoln mentioned M. I. Smith, who worked with promin and streptomycin in tuberculosis of the guinea pig. Recently, Feldman has found that a combination of streptomycin with p-aminosalicylic acid is more effective than either substance alone in experimental tuberculosis of the guinea pig. The same combination has been found highly effective in tuberculosis of the mouse. A possible explanation of the greater effectiveness of combined therapy may lie in a consideration of the data presented in a recent paper published in the Journal of Bacteriology. The author showed that the use of a mixture of streptomycin and sulfadiazine on a staphylococcus in vitro prevents the development of drug fastness

to either drug. Should this be confirmed and extended to other combinations it may offer a lead to the understanding of the beneficial effects of combined chemotherapy.

Dr. Perrin H. Long: I have been very much interested in Dr. Lincoln's paper tonight because the sulfones are quite active compounds, especially diamino diphenyl sulfone. Ten years ago it seemed to us that possibly they might be effective in subacute bacterial endocarditis. We treated four patients with this compound, and within a week we had retreated hastily from our position because immediately three patients developed acute hemolytic anemia. I would like to ask Dr. Lincoln a question. She said her patients developed cyanosis. This was the thing which should have tipped us off ten years ago, that we might get into difficulties because I have never seen people become quite so blue within twenty-four hours as the individuals to whom we gave diamino diphenyl sulfone. I want to ask first if these people became anemic from the promizole; secondly, in respect to the ataxia which these children developed, I have wondered what has happened to that particular sign after streptomycin was discontinued, because it is one of the most serious toxic reactions I think that has been noted. Certainly this has been true in the individuals in the veterans' group, and I am not sure that it is not as serious as the deafness which has been reported. After all, if you are deaf you can walk around and get out. Some of these ataxic individuals have learned to accommodate in the daytime, but don't dare go out in the dark because they will promptly fall down. Has the ataxia disappeared after treatment with streptomycin has been stopped?

Dr. Edith M. Lincoln: The ataxia bothered us a great deal at the beginning but the children seem to get used to it very easily. I think there is no doubt about it that there is damage to the nerves, actual destruction, but they adjust to it. This one little boy I told you about, the four year old, had to be sent home because he was so active, although he was so ataxic in the early stages that he was just weaving up and down the ward and would invariably fall. Before he left the hospital he could climb on top of the cubicles with just as much agility and dexterity as any child. That happened with all the patients that we had.

Dr. Francis F. Schwentker: I would like to know what happens to the tuberculin test after these children are under treatment.

Dr. Lincoln: The tuberculin tests in all cases that we have done have remained positive after promizole therapy.

Dr. Schwentker: I wondered whether there would be an increase or decrease in the size of the tuberculin reaction during therapy. Products of the killed tubercle bacilli might absorb the antibody and cause a decrease in the amount of reaction.

Dr. Lincoln: I am afraid we haven't tried that. In fact we are a little afraid of too many perifocal reactions around a cortical focus. We have done patch tests on children who have recovered. We expect, from the fact that the primary focus is visible for such a long time, that we shall have none which revert to negative.

Dr. Frederic B. Bang: I would like to ask Dr. Lincoln if any of her patients developed a red color of the urine.

Dr. Lincoln: We have seen red color in the urine. This happens not infrequently and the cause has not been identified. In fact, the Parke-Davis directive warned us of this color and we have paid very little attention to it.

Dr. A. Murray Fisher: I would like to ask if the promizole is excreted in the spinal fluid, and also if the organisms have become resistant to streptomycin. Probably Dr. Lincoln hasn't had more than one or two relapses in which she has been able to obtain the organisms the second time. I wondered if they became resistant.

Dr. Lincoln: We have made no study on promizole excreted in the spinal fluid at all. Unfortunately, we haven't been able to do much study on resistance either because none of our children except one have relapsed and have had to be treated a second time. We rely in large part on the clinical reaction. I think if this small boy gets over the meningitis relapse after treatment for a second time, the chances are that his organisms are not resistant to streptomycin. None of the original cases of miliary tuberculosis relapsed, so we were not able to do resistance studies with promizole. We had one child who had a marked anemia. We also had one who had miliary tuberculosis and became deeply jaundiced. We thought he probably had tuberculosis of his liver and his jaundice was associated with that; whether it was due to that or to a toxic reaction to promizole I don't know. Two of them did have leucopenia which did not respond to folic acid or any other treatment, and which cleared spontaneously.

BOOK REVIEWS

Advances in Pediatrics, Vol. 2. Editors: S. Z. Levine, Allan M. Butler, L. Emmett Holt, Jr., and A. Ashley Weech. Illus. 407 pp. $6.75. *Interscience Publishers, Inc., New York, New York*, 1947.

The volume of current medical literature has become so great that it has become practically impossible for one to keep abreast of the progress being made in many diverse fields. The need is being met by the publication of reviews or short monographs by authorities who are capable of reviewing, evaluating and bringing up to date the work on a particular subject. *Advances in Pediatrics* is published annually as a small volume with this objective. After the first issue in 1942 the publication was suspended during the war. Volume 2 has now appeared under new editorship. It fulfills its purpose excellently in presenting discussions by recognized authorities on pediatric subjects selected because of contemporary interest and importance. Its merits can be demonstrated best by listing the table of contents and authors:

Etiology of Congenital Malformations, by Josef Warkany
Acute Infectious Lymphocytosis, by Carl H. Smith
Role of Fluorine in Prevention and Treatment of Dental Caries, by H. Trendley Dean
The Treatment of Purulent Meningitis, by Hattie E. Alexander
Chemotherapy: Penicillin, Sulfonamides, Streptomycin and Tyrothricin, by Paul György and Henry F. Lee
Atypical Pneumonia, by John H. Dingle
Endocrine and Other Factors Determining the Growth of Children, by Nathan B. Talbot and Edna H. Sobel
Virus Diarrhea, by Katherine Dodd
Prematurity, by Harry H. Gordon
The Genesis of Physiologic Hyperbilirubinemia, by A. A. Weech
Prevention of Recurrences of Rheumatic Fever, by Ann G. Kuttner

The value of the volume is enhanced by abundant references which have been well indexed.

L. W.

Essentials of Pharmacology. By Frances K. Oldham, F. E. Kelsey, and E. M. K. Geiling. Illus. 440 pp. $5.00. *J. B. Lippincott Company, Philadelphia, Pennsylvania*, 1947.

This book from the University of Chicago, Department of Pharmacology, presents in brief fashion the pharmacological principles of drugs in current clinical use. In general, each chapter consists of a short discussion of a group of drugs, usually with the inclusion of structural formulas, followed by a list of official preparations and a selected bibliography. The therapeutic concepts are in excellent conformity with modern formulations. Emphasis has been placed upon the most

recent pharmacological developments, so that the book is amazingly up to date. The inclusion of all the latest advances has been accomplished partly at the expense of older fundamental work, and the presentation is thus somewhat unbalanced. The same comment may be made about the bibliographies.

The defects of this volume are chiefly those consequent upon the attempt to compress a large field into a small book. The discussions of the individual drugs are insufficiently detailed to tell the reader how to apply the information to clinical situations. Hence, the appeal of this book will be largely to those who are relatively unfamiliar with modern pharmacology and who desire a rapid introduction. It could not serve as a medical school text except for the purposes of review, or as a supplement to more extensive but less contemporary works. The physician will find it useful only for bibliographic material and chemical structures of recently introduced drugs.

C. G. Z.

Expectant Motherhood. 2nd Edition revised. By NICHOLSON J. EASTMAN. 198 pp. $1.50. *Little Brown and Company, Boston, Massachusetts*, 1947.

Advice books about pregnancy antedate the printed page, and if all were placed side by side a large library would result. Among the most widely read of the modern era is Dr. Eastman's *Expectant Motherhood*, first printed in 1940. During the succeeding seven years it was reprinted fifteen times and currently appears completely revised.

Expectant Motherhood is written for the intelligent layman. The author captivates the reader by his authoritative, sincere, simple style; a style devoid of window dressing. A great amount of valuable, practical information is packed into the small volume. If one were to offer any general criticism, he might take the author to task for the almost complete absence of historical data, a field in which the author has frequently demonstrated his special competence. The only excursion into medical history which he has allowed himself is a few paragraphs concerning the origin of obstetrical forceps. The reviewer feels that medical books written for the layman should not only present the essential facts but the historical evolution of their acquisition. Such a combination educates the public in an appreciation of modern scientific medicine, plus better understanding of its peripheral quackery.

Several new chapters have been added to the first edition. One of these is an excellent chapter on weight control in pregnancy with sample menus. "How to telephone your doctor" is an intriguing inclusion; its purpose is to make telephone consultations more efficient and satisfactory. Paragraphs on the much discussed Rh factor and on controversial caudal anaesthesia first appear in the revised edition.

In one instance Dr. Eastman allows faith in democracy to outweigh scientific critique. Because 84 per cent of seventy-five obstetrical authorities assume that smoking and inhaling twenty-five or more cigarettes daily have an unfavorable

effect on maternal health, he too implies this is the case. Yet neither he nor the other authorities offer scientific data to support this prejudice.

All in all *Expectant Motherhood* does an excellent job. Dr. Eastman makes a painstaking attempt to replace the subtle fears and folk misinformation of the pregnant woman and her kin by calm assurance and scientific knowledge. And he succeeds.

A. F. G.

Office Endocrinology. 3rd Ed. By ROBERT B. GREENBLATT. Illus. 303 pp. $4.75. *Charles C. Thomas, Springfield, Illinois*, 1947.

This is a well-intentioned effort to bring together into a single small volume the confusing theories and the treatment of certain endocrine problems. The author has had extensive experience in this field, both in the laboratory and clinically. His interest has been centered primarily in female endocrinology, and the book should more properly be given this title. Except for a short section of 27 pages on male endocrinology and 32 pages on the action of hormones and the available commercial products, the entire book is concerned with gynecological endocrinology. The author, in his preface to this edition, emphasizes that it has been prepared "for the practicing physician with the usual office equipment and with the laboratory facilities afforded by the average community hospital."

Were the general practitioner to follow through chronologically the advice on diagnosis and treatment as outlined under the various headings, he would in many instances be hopelessly at sea and the patient's pocketbook would be severely depleted. No mention is made of the necessity of a diagnostic curettage and cervical biopsy before endocrine therapy is instituted in menometrorrhagia. In the conclusion of this chapter this advice is given in case the woman is over 36 years of age. Far too many early malignancies are missed now because the pharmaceutically advised general practitioner resorts to shots before he performs a pelvic examination. The physician who performs suction curettage "30 or 40 days after the last menstrual period" as advised in case of amenorrhea may be considerably chagrined when he studies the tissue sections. His suggestion to use testosterone in bleeding associated with myomas of the uterus can only be applicable in the very rare instance. In Chapter 16 the shortcomings of anterior pituitary extracts, equine gonadotropins, and chorionic gonadotropins as producers of ovulation in the human ovary are stressed, yet he strongly advocates their use in the chapter "The Management of Sterility". Leucoplakia of the vulva is not mentioned in the chapter on Pruritis Vulvae.

The chapters on the various hormones, their physiologic properties and their commercial names and dosages are especially informative and useful. He is particularly cautious in the part on male endocrinology, and for this reason the advised treatments, though in many instances controversial, are more rational.

The problems of obesity and thyroid disease are inadequately treated, whereas the less common problems of sexual libido and sexual infantilism in the female

are extensively and well covered. There is a chapter entitled "Endocrine Headaches", which is diffuse and confusing, and might well have been omitted.

Clinical endocrinology is still an infant, and the shortcomings of this book are less the fault of the author than the inherent impossibility of the task he has set for himself. Many chapters contain material too controversial or poorly founded to be included in a working handbook for the undiscriminating, busy practitioner, who, in the words of the author's preface, "cannot keep up with rapid advances in the field nor is (he) interested in the polemics of why and wherefore". Inevitably this volume will encourage the practitioner of this description in the indiscriminate use of potent endocrine agents, though this is not the intent of the author.

R. B. S.
B. F. J.

Osteotomy of the Long Bones. By HENRY MILCH. Illus. 294 pp. $6.75. *Charles C. Thomas, Springfield, Illinois,* 1947.

Dr. Milch has done an excellent piece of work on a rather special aspect of orthopedic surgery. Following an interesting historical view of osteotomy, he develops his views on its objective and proceeds to describe lineal, tortional, transpositional, and angulational osteotomies of the long bones, such as the forearm, humerus, tibia, and fibula which he considers as straight bones because their axes are essentially in one plane.

He develops the osteotomy of the femur as a special feature in the second part of this book because of "that particular axial displacement of the femur which occurs in the coronal plane". There is much very valuable information in this concise work, and the charts of expected growth in children are especially valuable. He has applied a good deal of intelligent thought and wide experience. His views and methods will not, of course, gain unanimous approval, but his work is definitely worthwhile. "Osteotomy of the Long Bones" should be a valuable aid to the surgeon who must consider equalization of length or correction of deformity or dysfunction.

W. R. F.

Physiology of Man in the Desert. By E. F. ADOLPH AND ASSOCIATES. Illus. 357 pp. $6.50. Interscience Publishers, Inc., New York, New York, 1947.

The exigency of the war period turned the efforts of many investigators into the field of environmental physiology. This book reports the extensive investigations of the University of Rochester Desert Unit made during four years of arduous field and laboratory study of man's response to heat. There is presented a wealth of data, much of it graphically, on heat exchange, sweat formation, water turnover, blood constituents, urinary salt and water excretion, and circulatory responses to heat exposure. Quantitative measurements of water deficit are correlated with clinical manifestations. Important observations are recorded relative to the mechanism of thirst. Much of the data have led to the formulation of useful rules for the maintenance of life and maximum efficiency in desert environ-

ments. There are also many observations on over-all water metabolism which may be applied directly to related clinical problems.

Dr. Adolph and his collaborators have written a most entertaining and valuable account of a very dry subject. The numerous charts and maps add great clarity to the presentation. The purpose served by the photographs is obscure.

J. L. L., Jr.

Treatment of Diabetes Mellitus, The. 8th Ed. By ELLIOTT P. JOSLIN, HOWARD F. ROOT, PRISCILLA WHITE, ALEXANDER MARBLE, AND C. CABELL BAILEY. Illus. 861 pp. $10.00. *Lea & Febiger, Philadelphia, Pennsylvania,* 1946.

This standard text in the field of diabetes has been brought up to date by Joslin and his coworkers. The title is somewhat misleading since a large part of the book is concerned with etiology, diagnosis, pathology, and various complications of diabetes. The chapter on experimental diabetes produced by alloxan is well written.

There are numerous minor errors as is inevitable in so extensive a work. For example, on page 716, in discussing Cori's recent experimental observation of pituitary extract antagonism to insulin, pituitrin is referred to when, of course, anterior pituitary extract is meant; on page 153 the statement about blood galactose curve following oral administration of sugar is confusing; there might be disagreement with the statement on page 305 that normally the serum phosphorus is between 2 and 3 mg. per 100 cc.—but these are relatively minor points.

This book has long been of great value as a reference text. A wealth of material is covered, and numerous references are accurately recorded. Most of the chapters are well written and easy to read. The authors deserve much credit for the painstaking manner in which they have covered the field.

H. F. K., Jr.

Clinical Neuro-Ophthalmology. By FRANK B. WALSH. Illus. 1532 pp. $15.00. *The Williams and Wilkins Company, Baltimore, Maryland,* 1947.

This volume by Doctor Walsh represents years of profound study of clinical neuro-ophthalmology. It is a good deal more than a textbook—it is practically a compendium of information. The illustrations throughout are excellent. The text is clear and the references adequately cover the field.

The domain of the book extends, however, considerably beyond the range of the usual clinical neuro-ophthalmology. There are chapters on infections, ocular syphilis, familial degenerative diseases, toxic and metabolic diseases, etc. It might have been somewhat easier for the reader had this splendid book been separated into two volumes, one being limited to neuro-ophthalmology and the other to ophthalmic conditions which at times produce neuro-ophthalmological symptoms. The book is saved from confusion by its splendid index which enables the reader to follow the subject rapidly to its conclusion through its various ramifications.

This book belongs in the library of every ophthalmologist and neurologist. It is a splendid piece of work.

A. C. W.

Gifford's Textbook of Ophthalmology, 4th Ed. By FRANCIS H. ADLER. Illus 512 pp. $6.00. *W. B. Saunders Company, Philadelphia, Pennsylvania*, 1947.

This book by Doctor Adler purports to be a re-editing of the late Doctor Gifford's well-known textbook. As a matter of fact, it is far more than that. Virtually, it is a completely new textbook on ophthalmology, especially designed for students, embodying somewhat the general form of Doctor Gifford's book. This book is not only an admirable volume for students or beginners in ophthalmology, but will also be definitely helpful to internists and physicians, who seek a clear-cut description and explanation for the various ocular anomalies which they constantly encounter.

The description of medical ophthalmology throughout is remarkably good, clear and comprehensive. At the end of each chapter is a small but well selected bibliography which will enable the student to explore further any subject in which he may be especially interested.

If any criticism is to be made of this book, it might be the undue attention devoted to disturbances in ocular motility. However, the author is especially interested in this field, in which he has made outstanding advances.

This is not only a good book; it is probably the best small textbook on modern ophthalmology.

A. C. W.

Textbook of Bacteriology, A. By THURMAN B. RICE. 4th Ed. Illus. 603 pp. $6.50. *W. B. Saunders Co., Philadelphia, Pennsylvania*, 1947.

According to the author's prefaces this book "is not intended to serve as a manual for the determination of the identity of species. It is intended as a basis for the understanding of disease, to the end that diagnosis, prognosis, treatment and general management may be as efficient as is possible." "The technical processes described in detail are only those which may be done by the practicing physician, limited as he is in time, material, and equipment. When more is needed, he is instructed only in the manner of taking the sample, of sending it to the laboratory, and of interpreting the results." It is the opinion of the reviewer that the object stated in the second quoted sentence is unattainable under the limitations stated in the other sentences quoted. It is our opinion that a textbook should not be merely a brief outline of what the student is expected to learn and retain, but a book which can be used for reference during subsequent studies and practice.

The author seldom refers to original work and gives practically no references to literature. In justification he states—"It has been our experience that students do not use the bibliographies given in textbooks." Our experience has been otherwise. Different attitudes on the part of students can be cultivated by differences in teaching. In the long run mere epiricism may be less *practical* than habits of scholarship.

We would regard the book as inadequate for the minimum requirements of a medical student.

J. H. B.

BOOKS RECEIVED FOR REVIEW

Clinical Examination of the Nervous System, 8th ed. By G. H. MONRAD-KROHN. Illus. 380 pp. $4.50. *Paul B. Hoeber, Inc., New York, New York*, 1947.

Clinical Neuro-Ophthalmology. By FRANK B. WALSH. Illus. 1532 pp. $15.00. *The Williams and Wilkins Company, Baltimore, Maryland*, 1947.

Diagnosis in Daily Practice. By BENJAMIN V. WHITE AND CHARLES F. GESCHICKTER. Illus. 693 pp. $15.00. *J. B. Lippincott Company, Philadelphia, Pennsylvania*, 1947.

Diseases of the Nose, Throat and Ear. By WILLIAM L. BALLENGER, HOWARD C. BALLENGER, AND JOHN J. BALLENGER, 9th ed. Illus. 993 pp. $12.50. *Lea & Febiger, Philadelphia, Pennsylvania*, 1947.

Foot and Ankle, The, 3rd Ed. By PHILIP LEWIN. Illus. 847 pp. $11.00. *Lea & Febiger, Philadelphia, Pennsylvania*, 1947.

Fundamentals of Immunology, 2nd Ed. By WILLIAM C. BOYD. Illus. 503 pp. $6.00. *Interscience Publishers, Inc., New York, New York*, 1947.

George Crile—An Autobiography. Edited by GRACE CRILE. 2 vols. Illus. 624 pp. $10.00. *J. B. Lippincott Company, Philadelphia, Pennsylvania*, 1947.

Nursing in Modern Society. By MARY ELLA CHAYER. 288 pp. $4.00. *G. P. Putnam's Sons, New York, New York*, 1947.

P–Q–R–S–T: A Guide to Electrocardiogram Interpretation. By JOSEPH E. F. RISEMAN, 2nd Ed. Illus. 84 pp. $3.50. *The MacMillan Company, New York, New York*, 1947.

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Selected Writings of Benjamin Rush. Edited by DAGOBERT D. RUNES. 433 pp. $5.00. *Philosophical Library, New York, New York*, 1947.

Surgical Disorders of the Chest. By J. K. DONALDSON. Illus. 485 pp. $8.50. *Lea & Febiger, Philadelphia, Pennsylvania*, 1947.

Textbook of the Ear, Nose and Throat, 2nd Ed. By FRANCIS L. LEDERER AND ABRAHAM R. HOLLENDER. Illus. 596 pp. $7.00. *F. A. Davis Company, Philadelphia, Pennsylvania*, 1947.

Unipolar Lead Electrocardiography. By EMANUEL GOLDBERGER. Illus. 182 pp. $4.00. *Lea & Febiger, Philadelphia, Pennsylvania*, 1947.